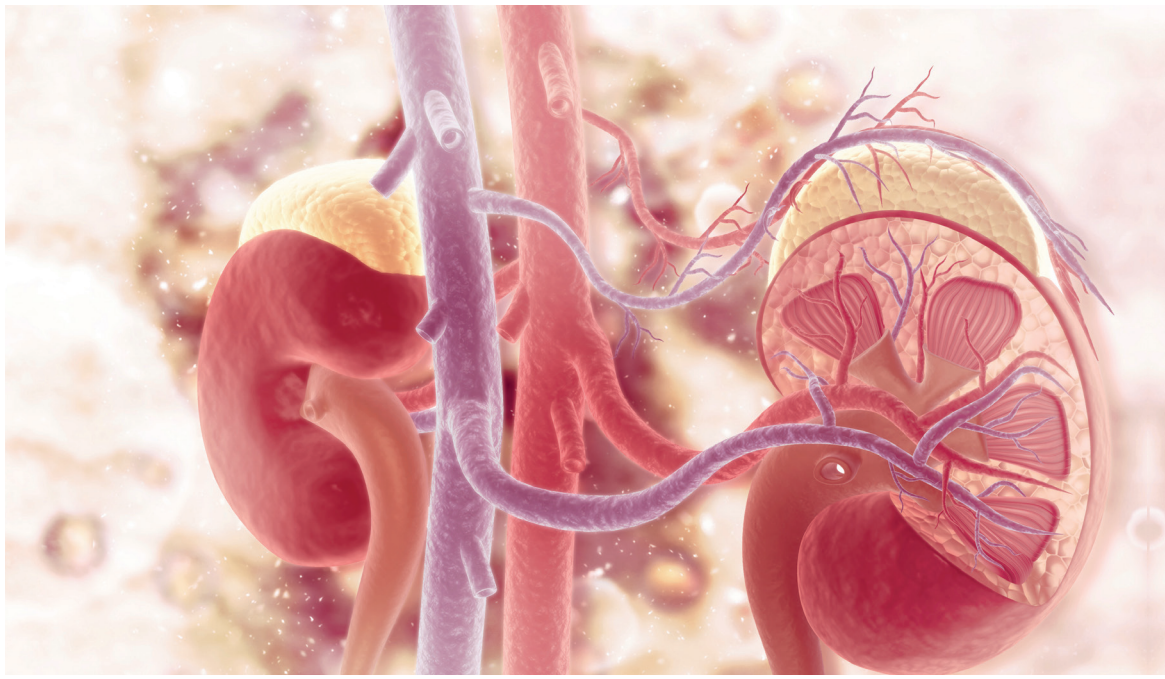
Volume 16
Number 4
Year 2023

ISSN 2720–2771
e-ISSN: 2720–4189

Renal Disease and Transplantation Forum



www.journals.viamedica.pl/renal_disease_and_transplant

VIA MEDICA

Renal Disease and Transplantation Forum

JOURNAL OF THE POLISH SOCIETY OF CHILD NERPHOLOGY
THE POLISH NEPHROLOGICAL NURSE SOCIETY
THE POLTRANSPLANT
THE POLISH SOCIETY OF NEPHROLOGY

Renal Disease and Transplantation Forum (ISSN 2720–2771; e-ISSN: 2720–4189) is published four times a year by

VM Media Group sp. z o.o., Grupa Via Medica
ul. Świętokrzyska 73, 80–180 Gdańsk, Poland
Phone: (+48 58) 320 94 94, fax: (+48 58) 320 94 60
e-mail: redakcja@viamedica.pl,
http://www.viamedica.pl, wap.viamedica.pl

22-6141.004.001

Editorial Address

Katedra i Klinika Nefrologii, Transplantologii i Chorób Wewnętrznych
Gdański Uniwersytet Medyczny
ul. Smoluchowskiego 17, 80-214 Gdańsk
phone: (58) 584 4700, fax: (58) 584 4746
e-mail: nerka@gumed.edu.pl

Renal Disease and Transplantation Forum

JOURNAL OF THE POLISH SOCIETY OF CHILD NERPHOLOGY
THE POLISH NEPHROLOGICAL NURSE SOCIETY
THE POLTRANSPLANT
THE POLISH SOCIETY OF NEPHROLOGY

2023, vol. 16, no. 4

RECOMMENDATIONS, STANDARDS AND OPINIONS

REVIEW ARTICLE

CASE REPORT

PAGES FORM HISTORY

Renal Disease and Transplantation Forum
2023, vol. 16, no. 3, 113–119

ISSN 2720–2771
e-ISSN: 2720-4189
DOI: 10.5603/rdtf.98440

Magdalena Jankowska[1], Alicja Dębska-Ślizień[1], Magdalena Krajewska[2], Katarzyna Krzanowska[3], Ilona Kurnatowska[4], Magdalena Durlik[5], Mariusz Niemczyk[6], Jolanta Małyszko[7], Tomasz Stompór[8], Paweł Stróżecki[9], Beata Naumnik[10], Ryszard Gellert[11], Andrzej Więcek[12], Andrzej Oko[13], Wojciech Załuska[14], Michał Nowicki[15], Jacek Różański[16]

[1]Department of Nephrology, Transplantation and Internal Medicine, University Clinical Center in Gdańsk, Poland
[2]Department of Nephrology and Transplantation Medicine, Wrocław Medical University, Poland
[3]Clinical Department of Nephrology, Dialysis and Transplantation Medicine, University Hospital of Kraków
[4]Department of Internal Medicine and Transplant Nephrology, Medical University of Łódź, Poland
[5]Department of Transplantation Medicine, Nephrology and Internal Medicine, Medical University of Warsaw
[6]Department of Immunology, Transplantation and Internal Medicine, Infant Jesus Clinical Hospital in Warsaw
[7]Department of Nephrology, Dialysis and Internal Medicine, Warsaw Medical University
[8]Department of Nephrology, Hypertensiology and Internal Medicine, University of Warmia and Mazury in Olsztyn
[9]Department of Nephrology, Hypertension and Internal Medicine, Nicolaus Copernicus University in Toruń, Poland
[10]1st Department of Nephrology and Transplantation Medicine with Dialysis Center, Medical University of Białystok
[11]Department of Nephrology and Internal Diseases, Centre for Postgraduate Medical Education in Warsaw
[12]Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia in Katowice, Poland
[13]Laboratory of Renal Disease Immunopathology and Tissue Compatibility, Poznań University of Medical Sciences, Poland
[14]Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia in Katowice, Poland
[15]Department of Nephrology, Hypertension and Kidney Transplantation, Clinical and Didactic Centre, Medical University of Łódź, Poland
[16]Department of Nephrology, Transplantation and Internal Medicine, Pomeranian Medical University in Szczecin, Poland

Principles of using tolvaptan in the treatment of patients with autosomal dominant polycystic kidney disease (ADPKD). Recommendations of the Working Group of the Polish Society of Nephrology

Abstract

Tolvaptan, a vasopressin type 2 receptor antagonist, is currently the only disease-modifying drug available for autosomal dominant polycystic kidney disease (ADPKD). The following recommendations discuss patients' eligibility for tolvaptan treatment and its monitoring while providing a practical supplement to the Summary of Product Characteristics of the medicinal product Jinarc (Otsuka).

Key word: cysts, vaptans, aquaresis, pharmacotherapy

INTRODUCTION

Authorization of tolvaptan for the treatment of rapid progression of autosomal dominant polycystic kidney disease (ADPKD) issued by the European Medicines Agency (EMA, 2015) has changed the disease management policies in countries where reimbursement for the treatment has been provided. Thanks to the Ministry of Health's drug program (B.126), Poland has joined the list of these countries in 2021. Tolvaptan is the first disease-modifying drug available for ADPKD treatment. Previous recommendations for the management of ADPKD patients, outlined in the document of the Polish Society of Nephrology Working Group 2019 [1], were limited to nephroprotection and management of complications. Therefore, with the introduction of the B.126 program, it became necessary to develop new recommendations for the treatment of this inherited disease.

Address for correspondence:
Magdalena Jankowska
Department of Nephrology,
Transplantology and Internal Medicine
Faculty of Medicine,
Medical University of Gdańsk
M.Skłodowskiej-Curie 3a Street
81-211 Gdańsk, Poland
magdalena.jankowska@gumed.edu.pl

Tolvaptan's mechanism of action involves binding to the vasopressin type 2 receptor (V2R) to block its activation (Fig. 1) [2]. V2 receptors are mainly located within the distal parts of the nephrons, where, when stimulated by vasopressin, they promote reabsorption of free water to exert an antidiuretic effect. Blocking V2R leads to aquaresis or electrolyte-sparing excretion of free water. Through the association of this receptor with adenylyl cyclase, a vasopressin-dependent increase in cyclic adenosine monophosphate (cAMP) levels is consequently blocked. cAMP controls numerous intracellular signaling pathways that promote cell proliferation, inhibition of epithelial cell apoptosis, and secretion of fluid into the renal tubules [3]. ADPKD is characterized by increased activity of these pathways. Due to the very short half-life of vasopressin, its levels cannot be measured directly, therefore, copeptin level (C-terminal fragment of preprovasopressin released along vasopressin) is used for this purpose [4]. Higher levels of plasma copeptin were observed in ADPKD patients as compared to healthy subjects [5].

Two randomized trials (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes 3:4 Trial [TEMPO 3:4]) [6] and Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD [REPRISE]) [7] showed that tolvaptan inhibits the increase in kidney size and the decrease in estimated glomerular filtration rate (eGFR) in patients presenting with early (eGFR > 60 mL/min/1.73 m^2) and advanced (eGFR 25–65 mL/min/1.73 m^2) stages of the disease. Data from both studies, as well as from another long-term observational study [8], indicate a consistent and sustained effect of tolvaptan in slowing eGFR decrease by about 1 mL/min/1.73 m^2 per year as compared with the placebo group. By extrapolating the data from the aforementioned studies, we predict that starting tolvaptan treatment at an eGFR of about 60 ml/min/1.73 m^2 may delay the onset of end-stage renal failure by about seven years [9].

Tolvaptan (available in Poland under the trade name Jinarc) is indicated for the treatment of rapid progression of ADPKD. Rapid progression is defined, in Europe, as the need for renal replacement therapy before the age of 58, i.e. earlier than in the case of most ADPKD patients according to the natural history of the disease [9].

These recommendations provide a practical supplement to the Summary of Product Characteristics (SmPC) of the medicinal product Jinarc (Otsuka) [10] and are based on published data from large centers with experience in treating ADPKD as well as on the opinions of experts providing ADPKD treatment in Poland.

RECOMMENDATION 1

We recommend that the rate of disease progression be assessed in all patients diagnosed with ADPKD earlier than 55 years of age and presenting with eGFR greater than 25 mL/min/1.73 m^2 of body surface area. We recommend that the appropriateness of assessing progression in patients above the age of 55 be decided on a case-by-case basis.

The rules for diagnosing ADPKD were presented in an earlier 2019 Polish Society of Nephrology Working Group document [1].

The benefits of tolvaptan treatment in ADPKD patients with rapid disease progression, as outlined in the introduction, justify the need to provide treatment options to every patient with this diagnosis. Although patients with rapid progression represent a small subgroup of the ADPKD population, screening should be performed in all patients to select the group that could benefit from therapy as early as possible. Early initiation of tolvaptan treatment ensures cumulative benefits over time.

As shown by the results of the REPRISE trial [7], no difference in eGFR was observed between tolvaptan-treated and placebo-treated patients over the age of 55. Because in that study the group of patients at the age of > 55 years was small, it cannot be ruled out that individual patients with rapid disease progression may benefit from the treatment. The B.126 drug program does not limit access to the treatment based on age, and, therefore, in motivated patients without concomitant diseases that might affect eGFR through other mechanisms (e.g., diabetes, heart failure), evaluation of the rate of ADPKD progression may be warranted. The inclusion of the drug in this age group may offer a chance to avoid renal replacement therapy. Extending the time of conservative treatment may also, in selected cases, facilitate finding a kidney donor and anticipatory transplantation.

Table 1. Possible rapid progression of ADPKD in patients older than 39 years, based on eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [11].

Age in years	eGFR (mL/min/1.73 m²)
40–44	< 90
45–49	< 75
50–55	< 60

RECOMMENDATION 2

We recommend diagnosing rapid disease progression based on age, eGFR, and total kidney volume (TKV).

The consensus of the working group of the European Renal Association (ERA), the European Reference Network for Rare Kidney Diseases (ERKNet), and PKD International suggest that age and eGFR values are used in guiding diagnosis in ADPKD patients over 39 years of age, as presented in Table 1 [11]. In patients younger than 40, eGFR values are not useful to assess the likelihood of rapid progression. We recommend using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula to estimate rapid progression.

In patients with eGFR of < 90 m/ /min/1.73 m^2, rapid progression may be evidenced by:

- An eGFR decrease of at least 5 mL/ /min/1.73 m^2 within one year in the absence of other causes (such as acute kidney injury) that can be responsible for the progression; or
- An eGFR decrease of at least 2.5 mL/ /min/1.73 m^2 per year over five years of follow-up.

The aforementioned European consensus adopts the value of ≥ 3 mL/min/1.73 m^2 per year for 4 years provided that a minimum of 5 creatinine determinations are available from this period to facilitate determination of the eGFR decline curve [11]. Rapid progression is evidenced by a linear eGFR decline greater than that expected in the course of natural disease progression (> 2.5 mL/min/1.73 m^2 per year).

The assessment of ADPKD progression as based on eGFR values has several limitations. The first is its unsuitability in patients with normal eGFR. Another is that that method provides data on past disease progression. Many patients reporting for nephrological care have no history of creatinine determinations being made over such a long period. In ADPKD patients, the diagnosis of rapid progression should not involve waiting for 4–5 years.

An imaging study with TKV evaluation should be performed in every ADPKD patient. TKV can be calculated from an MRI scan without contrast or, in patients with eGFR > 60 ml/min/1.73 m^2, from a contrast-enhanced computed tomography (CT) scan. Prognostic significance is attributed to the height adjusted TKV value (htTKV) [12]. The B.126 program makes it possible to use the ultrasound-determined greater kidney length of > 16.5 cm as an inclusion criterion.

The best predictor of future progression is the Mayo imaging classification score, with the patient's age and htTKV taken into account. A calculator for this score is available for free at http://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754 [12]. To qualify the patient for the treatment, it is sufficient to use the htTKV value calculated using the ellipsoid method, in contrast to the much more time-consuming methods used to assess htTKV in research studies. Despite its unquestionable advantages, the Mayo classification is not widely available in Poland. We believe that efforts should be made to make it available at least in high-reference centers offering treatment for ADPKD patients.

In the absence of access to reliable htTKV measurements, one should assume that patients younger than 46 years of age presenting with normal renal function and htTKV of > 650 mL or renal length of > 16.5 cm as observed in ultrasound are at risk for rapid development of renal failure (experts' opinion).

RECOMMENDATION 3

In cases of ADPKD with an atypical course and when progression cannot be diagnosed using routine criteria (Recommendation 2), we recommend that additional prognostic factors (genetic testing, clinical risk factors, family history) be used.

In doubt, we suggest using other, more difficult-to-use tools to assess progression, such as the PRO-PKD (Predicting Renal Outcome in Polycystic Kidney Disease) classification [13] or the Mayo classification (Tab. 2, 3). In practice, this may mean referring the patient to a specialized center with capabilities for genetic testing or calculating TKV according to the Mayo method.

Table 2. Classification of ADPKD according to the Mayo criteria [12].

Mayo class	1A	1B	1C	1D	1E
TKV growth per year (%)	< 1.5	1.5	3 5	4.5	> 6
eGFR reduction per year (mL/min/1.73 m^2)	−0.1	−1.2	−2.5	−3.4	−4.6
Incidence of ESKD over 10 years (%)	2.4	11.0	37.8	47.1	66.9

CT — computed tomography; MRI — magnetic resonance imaging

Table 3. PRO-PKD scores for assessment of ADPKD prognosis [13].

Male: 1 point
Hypertension < 36 years of age: 2 points
First urological incident (macroscopic hematuria, back pain, cyst infection) < 35 years of age: 2 points
Pathogenic variant in PKD2 gene: 0 points
Pathogenic variant in PKD1 gene (missense)a: 2 points
Pathogenic variant in PKD1 gene (truncation)b: 4 points
A score of ≤ 3 excludes progression of PKD before the age of 60 (negative predictive value of 81.4%)
A score of > 6 is a predictor of rapid progression from ESKD before the age of 60 (positive predictive value of 90.9%)
Intermediate scores (4–6): prediction of progression uncertain

[a]Pathogenic variant resulting in an amino acid residue substitution
[b]Pathogenic variant resulting in a shorter protein product (due to a premature stop codon [nonsense mutations] or a change in the reading frame [frame--shift or splicing mutations]).

RECOMMENDATION 4

We recommend that tolvaptan treatment be offered to any patient meeting the criteria for rapid progression of ADPKD unless contraindications exist.

Any patient with rapid progression of ADPKD presenting with no contraindications for treatment as listed in the drug's SmPC should be provided with information about the benefits, risks (Tab. 4), and adverse effects of treatment with tolvaptan. The most common adverse effects include thirst, polyuria, nocturia, and pollakisuria as well as liver damage. The risk of anaphylaxis is unknown.

Tolvaptan should be given to all consenting patients with rapid disease progression who meet the criteria for inclusion in the drug program (Tab. 5).

In cases of patients with documented rapid disease progression who do not meet the criteria for inclusion in the drug program, we recommend that their physician attempt to obtain individual inclusion approval from the relevant National Health Fund branch.

RECOMMENDATION 5

We recommend aiming at the maximum daily dose (120 mg) or the maximum tolerated dose of tolvaptan.

The greatest benefit of the treatment is obtained after achieving full blockade of the V2 receptor. The majority of patients participating in the TEMPO 3:4 and REPRISE trials had received the maximum recommended dose of the drug (120 mg in two divided doses). At present, no tools are available to confirm the degree of V2R saturation with lower doses. Given the drug's pharmacokinetics, ensuring complete blockade of the V2R receptor for 24 hours is most likely possible with the highest dose of the drug.

The aquaretic effect should not be the reason for dose reduction or discontinuation of dose up-titration, as past observations indicate that the treatment tolerability improves over time. Patients should be informed of the potential benefits of maintaining the highest tolerated dose. Prescribing a reduced osmolytic load diet (limiting the quantities of sodium and simple sugars in the diet) usually alleviates the aquaretic effect. Earlier administration or reduction of the afternoon drug dose may have a beneficial effect in cases of intolerable nocturia.

Since tolvaptan is metabolized by cytochrome CYP3A, consumption of grapefruit juice is contraindicated during the treatment. Chronic use of moderate and strong CYP3A inhibitors requires a reduction in the daily tolvaptan dose.

Concomitant use of medicinal products that are moderate CYP3A inhibitors (e.g. amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil) or strong CYP3A inhibi-

Table 4 Benefits and risks of ADPKD treatment with tolvaptan

Benefits	Risks
Reduced rate of kidney enlargement	Polyuria, frequent urination, nocturia
Reduced rate of eGFR decline	The need to drink plenty of fluids
Delayed requirement for renal replacement therapy	Frequent laboratory checkups (1 × per month for the first 18 months)
Reduced kidney pain	Possibility of idiosyncratic liver damage
Reduced incidence of urinary tract infections	Fatigue
Reduced risk of urolithiasis	Drug interactions (CYP3A)
	Need for contraception in women of childbearing age

Table 5. Eligibility criteria for the B. 126 drug program (overall)

1) Diagnosis of the autosomal dominant form of polycystic kidney disease (ADPKD) based on MRI or ultrasound scans (Pei-Ravine criteria)a ;
2) Age ≥ 18 years;
3) Rapid disease progression defined as:
   (a) eGFR reduction of ≥ 5 mL/min/1.73 m^2 per year and eGFR of 30–90 mL/min/1.73 m^2;
   or
   (b) eGFR reduction of ≥ 2.5 ml/min per year over 5 years and eGFR 30–60 mL/min/1.73 m^2;
   or
   (c) total kidney volume (TKV) increase of > 5% per year on MRI or TKV of one of the kidneys of > 750 mL on MRI or the length of the larger kidney of > 16.5 cm on ultrasound.

[a]Below are standardized sonographic criteria for the diagnosis and exclusion of ADPKD, along with the positive (PPV) and negative (NPV) predictive values, as well as sensitivity (SEN) and specificity (SPEC) according to the original publication by Pei et al. [16]. Unlike the classic Ravine criteria, which showed adequate sensitivity only in patients with a pathogenic variant in the PKD1 gene, the presented standardized criteria can be applied to all patients, including those without a definitive genetic diagnosis. The cited data show that the sensitivity of the sonographic criteria is age-dependent and lower in younger people, especially those under 30 years of age. The criteria are not applicable to those under the age of 15.

Confirmation of diagnosis	PKD1	PKD2	No genetic diagnosis
Age and number of cysts required to confirm diagnosis			
15–29 ≥ 3 cysts*	PPV = 100% SEN = 94.3%	PPV = 100% SEN = 69.5%	PPV = 100% SEN = 81.7%
30–39 ≥ 3 cysts*	PPV = 100% SEN = 96.6%	PPV = 100% SEN = 94.9%	PPV = 100% SEN = 95.5%
40–59 ≥ 2 cysts in each kidney	PPV = 100% SEN = 92.6%	PPV = 100% SEN = 88.8%	PPV = 100% SEN = 90%
Exclusion of diagnosis	PKD1	PKD2	No genetic diagnosis
Age and number of cysts required to confirm diagnosis			
15–29 No cysts	NPV = 99.1% SPEC = 97.6%	NPV = 83.5% SPEC = 96.6%	NPV = 90.8% SPEC = 97.1%
30–39 No cysts	NPV = 100% SPEC = 96%	NPV = 96.8% SPEC = 93.8%	NPV = 98.3% SPEC = 94.8%
40–59 No cysts	NPV = 100% SPEC = 93.9%	NPV = 100% SPEC = 93.7%	NPV = 100% SPEC = 93.9%

NPV — negative predictive value; PPV — positive predictive value; SEN — sensitivity; SPEC — specificity
*unilateral or bilateral

tors (e.g. itraconazole, ketoconazole, ritonavir, clarithromycin) increases the risk of adverse effects and complications of tolvaptan treatment.

RECOMMENDATION 6

We recommend regular monitoring of the potential adverse effects of tolvaptan at least once a month during the first 18 months of treatment and at least once every 3 months beyond the first 18 months of treatment.

Hepatotoxicity associated with tolvaptan develops via an idiosyncratic mechanism and may occur in 5–10% of treated patients [14]. All documented cases of treatment-related increases in liver enzymes occurred within the first 18 months after treatment initiation [14]. Treatment should be discontinued if ALT or AST levels rise three-fold above the upper limit of normal [10].

In the first 3 months of treatment, a decrease in eGFR is expected and should be considered a marker of therapeutic efficacy [15].

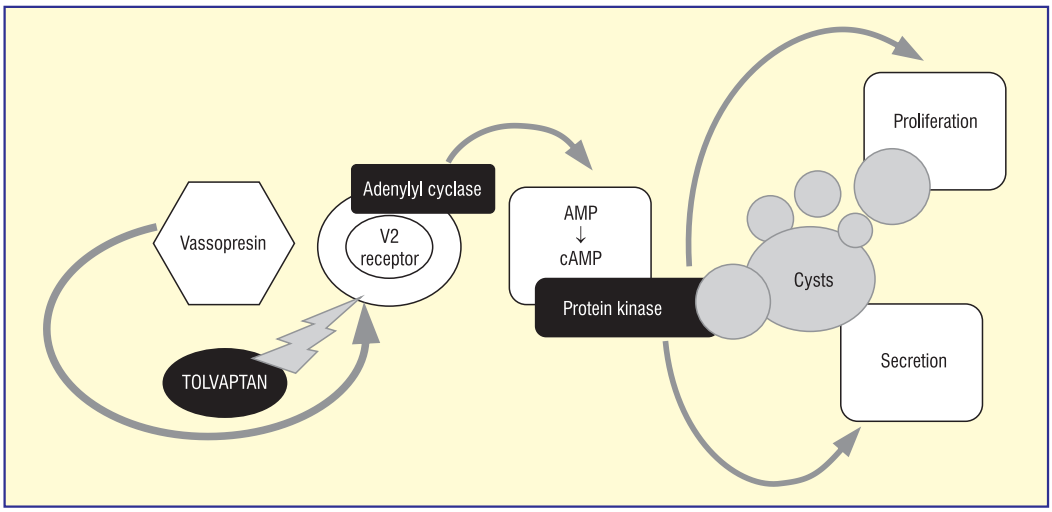


Figure 1. Simplified diagram showing the mechanism of tolvaptan's effect on ADPKD progression

A steady decline in eGFR values over the subsequent months of treatment and a decrease of more than 30% from baseline may suggest dehydration and require further diagnosis.

SUMMARY

The introduction of a V2R antagonist into the treatment regimens has changed management strategies in ADPKD patients. In every ADPKD patient, it is now necessary to rule out rapid disease progression. We recommend that the disease progression be assessed on the basis of age, eGFR, and TKV. Any patient meeting the criteria for rapid progression should be informed of the benefits and risks of tolvaptan treatment. Tolvaptan treatment should be started in all consenting patients with rapid ADPKD progression and no treatment contraindications if they meet the inclusion criteria for the B.126 drug program.

RULES

Evaluate the rate of progression in each patient.

Be mindful of the eGFR limits when qualifying for therapy.

Always evaluate TKV.

In rapid progression, include tolvaptan unless contraindications are present.

Aim at using the maximum tolerated dose of the drug.

Be mindful of possible interactions (CYP3A-mediated metabolism).

Monitor liver enzymes, hydration status, and natremia.

References

1. Dębska-Ślizień A, Jankowska M, Nowicki M, et al. Zasady postępowania z chorymi na autosomalnie dominujące wielotorbielowate zwyrodnienie nerek (ADPKD) i inne torbielowate choroby nerek . Nefrol Dial Pol. 2019; 23: 1–15.
2. Rinschen MM, Schermer B, Benzing T. Vasopressin-2 receptor signaling and autosomal dominant polycystic kidney disease: from bench to bedside and back again. J Am Soc Nephrol. 2014; 25(6): 1140–1147, doi: 10.1681/ASN.2013101037, indexed in Pubmed: 24556353.
3. Belibi FA, Reif G, Wallace DP, et al. Cyclic AMP promotes growth and secretion in human polycystic kidney epithelial cells. Kidney Int. 2004; 66(3): 964–973, doi: 10.1111/j.1523-1755.2004.00843.x, indexed in Pubmed: 15327388.
4. Meijer E, Bakker SJL, Halbesma N, et al. Copeptin, a surrogate marker of vasopressin, is associated with microalbuminuria in a large population cohort. Kidney Int. 2010; 77(1): 29–36, doi: 10.1038/ki.2009.397, indexed in Pubmed: 19847155.
5. Gansevoort RT, van Gastel MDA, Chapman AB, et al. TEMPO 3:4 Investigators. Plasma copeptin levels predict disease progression and tolvaptan efficacy in autosomal dominant polycystic kidney disease. Kidney Int. 2019; 96(1): 159–169, doi: 10.1016/j.kint.2018.11.044, indexed in Pubmed: 30898339.
6. Torres V, Chapman A, Devuyst O, et al. Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease. N Engl J Med. 2012; 367(25): 2407–2418, doi: 10.1056/nejmoa1205511.
7. Torres VE, Chapman AB, Devuyst O, et al. REPRISE Trial Investigators. Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease. N Engl J Med. 2017; 377(20): 1930–1942, doi: 10.1056/NEJMoa1710030, indexed in Pubmed: 29105594.

8. Edwards ME, Chebib FT, Irazabal MV, et al. Long-Term Administration of Tolvaptan in Autosomal Dominant Polycystic Kidney Disease. Clin J Am Soc Nephrol. 2018; 13(8): 1153–1161, doi: 10.2215/CJN.01520218, indexed in Pubmed: 30026287.
9. Chebib FT, Perrone RD, Chapman AB, et al. A Practical Guide for Treatment of Rapidly Progressive ADPKD with Tolvaptan. J Am Soc Nephrol. 2018; 29(10): 2458–2470, doi: 10.1681/ASN.2018060590, indexed in Pubmed: 30228150.
10. Charakterystyka produktu leczniczego - Jinarc. https://rejestrymedyczne.ezdrowie.gov.pl › rpl.
11. Müller RU, Messchendorp AL, Birn H, et al. An update on the use of tolvaptan for autosomal dominant polycystic kidney disease: consensus statement on behalf of the ERA Working Group on Inherited Kidney Disorders, the European Rare Kidney Disease Reference Network and Polycystic Kidney Disease International. Nephrol Dial Transplant. 2022; 37(5): 825–839, doi: 10.1093/ndt/gfab312, indexed in Pubmed: 35134221.
12. Irazabal MV, Rangel LJ, Bergstralh EJ, et al. CRISP Investigators. Imaging classification of autosomal dominant polycystic kidney disease: a simple model for selecting patients for clinical trials. J Am Soc Nephrol. 2015; 26(1): 160–172, doi: 10.1681/ASN.2013101138, indexed in Pubmed: 24904092.
13. Cornec-Le Gall E, Audrézet MP, Rousseau A, et al. The PROPKD Score: A New Algorithm to Predict Renal Survival in Autosomal Dominant Polycystic Kidney Disease. J Am Soc Nephrol. 2016; 27(3): 942–951, doi: 10.1681/ASN.2015010016, indexed in Pubmed: 26150605.
14. Watkins PB, Lewis JH, Kaplowitz N, et al. Clinical Pattern of Tolvaptan-Associated Liver Injury in Subjects with Autosomal Dominant Polycystic Kidney Disease: Analysis of Clinical Trials Database. Drug Saf. 2015; 38(11): 1103–1113, doi: 10.1007/s40264-015-0327-3, indexed in Pubmed: 26188764.
15. Akihisa T, Kataoka H, Makabe S, et al. Initial decline in eGFR to predict tolvaptan response in autosomal-dominant polycystic kidney disease. Clin Exp Nephrol. 2022; 26(6): 540–551, doi: 10.1007/s10157-022-02192-2, indexed in Pubmed: 35165806.
16. Pei Y, Obaji J, Dupuis A, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. J Am Soc Nephrol. 2009; 20(1): 205–212, doi: 10.1681/ASN.2008050507, indexed in Pubmed: 18945943.

Renal Disease and Transplantation Forum
2023, vol. 16, no. 4, 120–126

ISSN 2720–2771
e-ISSN: 2720-4189
DOI: 10.5603/rdatf.97835

Alicja Dębska-Ślizień[1], Magdalena Durlik[2], Marta Wawrzynowicz-Syczewska[3], Małgorzata Sobieszczańska-Małek[4], Robert Flisiak[5], Maciej Urlik[6]

[1]Department of Nephrology, Transplantology and Internal Diseases, Medical University of Gdańsk
[2]Department of Transplantation Medicine, Nephrology and Internal Diseases, Medical University of Warsaw
[3]Department of Infectious Diseases, Hepatology and Liver Transplantation, Pomeranian Medical University, Szczecin
[4]Department of Heart, Thoracic and Transplant Surgery, Advanced Heart Failure and Mechanical Support Subunit, Central Clinical Hospital of University Clinical Centre, Medical University of Warsaw
[5]Department of Infectious Diseases and Hepatology, Medical University of Białystok
[6]Department of Cardiac Surgery, Transplantology, Vascular and Endovascular Surgery, Silesian Medical University in Katowice, Silesian Centre for Heart Diseases in Zabrze

Recommendations for *herpes zoster* prevention in solid organ transplant recipients in Poland

Abstract

Herpes zoster (i.e. shingles) is a widespread infectious disease caused by reactivation of the varicella-zoster virus. Although the cutaneous manifestation of the disease is the most common, shingles is also associated with numerous complications, e.g. neurological, including postherpetic neuralgia. It is estimated that one-third of the general population will develop herpes zoster during their lifetime, and the incidence in solid organ recipients is even higher. What is more transplant recipients are more likely to suffer from severe complications of the disease. The most effective method of preventing herpes zoster is vaccination. The only vaccine recommended and available in Poland is recombinant adjuvanted zoster vaccine. Its safety and effectiveness were demonstrated in both the general adult population and solid organ recipients.

In this article, we present the position of experts in transplantation and infectious diseases on herpes zoster prevention in the solid organ transplant recipient population. The group includes kidney, liver, lung, and heart recipients.

Key words: herpes zoster prevention, solid organ transplant recipients, vaccination

INTRODUCTION

ETIOLOGY AND PATHOGENESIS

Herpes zoster (HZ, i.e. shingles) is an infectious disease caused by reactivation of the varicella-zoster virus (VZV, currently described as Human Herpesvirus-3 — HHV-3). The primary VZV infection, usually in the form of chickenpox, most commonly affects children. The primary disease occasionally occurs as an intrauterine infection or as a result of live zoster vaccination [1]. In the further course of the infection, when the immunity to VZV is established, the virus spreads along sensory neurons to the dorsal root ganglia. The infection then progresses to a latent form [2]. In immunocompromised or elderly patients, due to immune response disabilities, latent VZV infection reactivation may occur. The 10-year recurrence rate reaches up to 10% [3]. The virus travels antegradely to the skin nerve terminals and accesses epithelial cells causing clinically active *herpes zoster* [1, 4–5].

RISK FACTORS

The additional risk factors for developing *herpes zoster* are age ≥ 50 years, immunodeficiency (immunosuppression, human immunodeficiency virus [HIV] infection, malignancies, solid organ or hematopoietic stem cell trans-

Address for correspondence:
prof. dr hab. n. med. Alicja Dębska-Ślizień, Department of Nephrology, Transplantology and Internal Diseases, Medical University of Gdańsk, e-mail: adeb@gumed.edu.pl

plantation), and additional comorbidities (e.g. cardiovascular disease, chronic liver disease, chronic kidney disease, chronic obstructive pulmonary disease, autoimmune diseases: systemic lupus erythematosus or rheumatoid arthritis, diabetes mellitus, inflammatory bowel disease, depression, bronchial asthma, physical trauma [e.g. surgery], COVID-19). The highest incidence rates apply to patients with hematological malignancies and patients with solid organ tumors (e.g. lung cancer). What is more, elderly patients with cancer have a 1.2–2.4-fold higher risk of developing HZ than those without malignancy [6–8].

EPIDEMIOLOGY

There is no obligation to report *herpes zoster* incidents in Poland; therefore, the exact number of cases is not known. Worldwide, the incidence of *herpes zoster* ranges from 1.2 to 3.4 cases per 1000 people per year. What is more, the incidence increases to 3.9–11.8 per 1000 people for people over 65 years of age. Most (95–97%) of the adult population is VZV-IgG-positive. Thus, it is estimated that one-third of the worldwide general population will develop *herpes zoster* during their lifetime [9].

CLINICAL MANIFESTATIONS AND COMPLICATIONS OF *HERPES ZOSTER*

Herpes zoster usually begins with prodromal non-specific symptoms such as hypersensitivity, itching, burning, or pain of the skin. It is followed by a vesicular rash along corresponding dermatomes (one or two unilateral dermatomes innervated by the same sensory nerve). The vesicles filled with serous content containing VZV particles transform into scabs within 2–4 weeks [10–11]. The rash most often develops on the trunk (in one-third it is located on the upper part of the trunk) [12]. In rare cases, the lesions may affect ≥ 3 dermatomes (disseminated form). Other manifestations are less common and are associated with severe course and complications. It is estimated that 8–20% of patients suffer from zoster ophthalmicus caused by reactivation of latent VZV in the trigeminal ganglion. The viruses spread through the ocular nerve causing lesions on the skin of the upper eyelid, the conjunctiva, and on the cornea itself. A possible complication of this form of the disease is painful ulceration that can lead to loss of eyesight [13].

Another form of *herpes zoster* is herpes zoster oticus involving the auricle (painful lesions on the earlobe), external auditory canal, or tympanic membrane. The possible complication of this form of the disease is hearing loss or persistent tinnitus. In rare cases, it manifests as Ramsay-Hunt syndrome which is defined by a triad of symptoms including unilateral ear pain, vesicles in the external auditory canal, and facial nerve palsy [14]. HZ is not always associated with visible skin lesions, e. g. the visceral zoster (presenting as abdominal pain, elevated liver enzymes, and hyponatremia often without visible skin lesions) may present with delayed or absent rash.

The most common symptom of *herpes zoster* is pain, which can be of inflammatory or neuropathic origin. The acute phase of pain lasts up to 30 days and the subacute phase 30–90 days. However, the most common long-term complication is chronic pain — post-herpetic neuralgia (PHN) defined as pain lasting for longer than 3 months. It is estimated that even up to 40% of patients may experience pain six months after the disease and 20% after 1 year. The incidence of PHN increases in the elderly patients to 60–70% [15]. This pain is most likely related to post-herpetic tissue damage and significantly affects patients' quality of life [16–18].

A recent publication identified also an increased incidence of myocardial infarction within the 30 days following *herpes zoster*. The additional risk factors described were previous history of myocardial infarction, male sex, age ≥ 50 years, history of heart failure, peripheral vascular disease, HIV infection, previous cerebrovascular incident, and renal disease [19].

THE COURSE OF *HERPES ZOSTER* AFTER SOLID ORGAN TRANSPLANTATION

The incidence rates of herpes zoster in immunocompromised or immunosuppressed patients are significantly higher in comparison to the age-adjusted healthy population [20]. That higher incidence is associated with reduced cellular immunity; thus, the viral replication is not inhibited properly, which causes susceptibility to VZV replication [21].

Several studies including patients after solid organ transplantation (SOT) demonstrate that the organ recipient population is at exceptional risk of developing HZ, including the severe, complicated, recurrent, and disseminated form. It is estimated that the *herpes zoster* incidence in adult SOT recipients is approximately 8–11% during the first

4 years post-transplantation [37]. In a cohort study, in 1077 eligible SOT recipients, the cohort-specific HZ incidence rate was 22.2 per 1000 patient-years (0.95 CI, 18.1–27.4). The highest HZ incidence was observed in heart transplant recipients (40.0 per 1000 patient-years [PY][95% CI, 23.2–68.9]) [22]. What is more, another study by Klo MML et al. including 1033 SOT recipients, indicated that, in addition to heart recipients, lung recipients are also at significant risk of HZ and its complications (38.8 per 1000 PY). In the case of older recipients, the lack of CMV (cytomegalovirus) prophylaxis and inductive therapy with anti-thymocyte globulin (ATG) were also shown as additional risk factors for HZ incidence after SOT [23]. The incidence of HZ in orthotopic liver transplantaion (OLTx) recipients is comparable between countries, ranging from about 16.3 to 22.7 per 1000 PY [24]. As with the above, the incidence of HZ in kidney recipients does not differ substantially between developed countries and ranges from 24.4 to 28.0 per 1000 PY [25].

The disseminated, ophthalmic, and facial form of HZ with the involvement of multiple dermatomes is more frequent in SOT recipients. Such complications as PHN, ocular complications (keratopathy, episcleritis, iritis, monocular blindness), cranial nerve involvement, or encephalitis occur on average in 31% [39% of heart transplantation (HTx), 47% of lung transplantation (LuTx), 20% of OLTx, 20% of kidney transplantation (KTx)] [23, 26].

VACCINATION AGAINST *HERPES ZOSTER* — SAFETY AND EFFECTIVENESS

The most effective method of preventing *herpes zoster* and its complications is vaccination; however, it is not intended for post-exposure prophylaxis or HZ treatment. Currently, two vaccines against *herpes zoster* are registered in the European Union (EU):

- live, attenuated herpes zoster vaccine (*Zostavax, ZVL*): registered in the USA and EU in 2006, currently unavailable in Poland. It is given subcutaneously in one dose. It can only be administered to immunocompetent individuals (healthy adults 50 years or older) as it contains replication-competent viruses. The efficacy in HZ prevention is 51%, and PHN prevention is 67% in an average 3-year post-vaccination follow-up [27]
- recombinant, adjuvanted zoster vaccine (*Shingrix, RZV*): subunit vaccine containing recombinant glycoprotein E in combination with adjuvant ($AS01_B$) to boost the immune response. Currently, it is the only recombinant vaccine available in Poland (registered in the EU in 2018, in Poland in 03.2023) for the prevention of *herpes zoster* and post-herpetic neuralgia in patients ≥ 50 years of age and those aged ≥ 18 years with increased risk of developing HZ. It is also preferred over the Zostavax vaccine. The vaccination schedule includes the intramuscular administration of 2 doses within 2–6 months.

The efficacy of the RZV vaccine is very high. It has been shown to reduce the risk of developing *herpes zoster* by 97.2% in adults ≥ 50 years of age and by 89.8% in adults over 70 years of age in 3-year follow-up. Moreover, vaccination with RZV decreased significantly the risk of PHN by 91.2% in people aged ≥ 50 years and by 88.8% in people aged ≥ 70 years [28, 29]. Vaccination also substantially reduced the duration of HZ-associated pain, its intensity, and the amount of used analgesic medications [30]. Recently published data have also shown a reduction in the likelihood of myocardial infarction in patients aged ≥ 50 years after vaccination against *herpes zoster* [19].

Most adverse reactions (AEs) after RZV vaccination were described as mild to moderate in intensity (such as fatigue or myalgia) with a median duration of 3 days. The incidence rate of severe AEs or death was similar to the placebo group [28, 29]. Immunization was associated with long-term protection, as demonstrated in 6-year follow-up. Specific antibody titer was shown to be 7.3-fold higher at month 72 post-vaccination, and the gE-specific cell-mediated immune response was 3.8-fold higher than the pre-vaccination value [31].

It is not necessary to confirm serological VZV-IgG status before vaccination against *herpes zoster*. The vaccine can be given to patients vaccinated against VZV in the past. In case of acute HZ, vaccination should be postponed for 12 months. There are no data on the requirement for booster doses.

VACCINATION AGAINST *HERPES ZOSTER* IN SOLID ORGAN TRANSPLANT RECIPIENTS

In SOT recipients, the immunosuppressive treatment causes a reduced B and/or T lymphocyte reaction; therefore, the humoral and cellular response to vaccination is suboptimal implying the insufficiency of specific immuni-

ty. The ultimate response to vaccination after transplantation depends also on many factors, such as the type and dosage of immunosuppression, the age of the recipient, or additional comorbidities. What is more, the antibodies produced after vaccination tend to disappear more rapidly in this group of patients; however, antibody titers before transplantation are a predictor of antibody titers after the procedure. The timing of vaccination appears to determine the crucial role of the immunization process, and it should ideally be carried out during the pre-transplantation waiting period (ZVL or RZV). Most vaccines appear to be safe in SOT recipients; however, live attenuated vaccines are contraindicated after transplantation due to the risk of developing vaccine-induced disease, and they should be given at least 4 weeks before transplantation. On the other hand, the safety, immunogenicity, and efficacy of the recombinant, adjuvanted vaccine have been demonstrated in groups at increased risk of developing HZ: autologous hematopoietic stem cell transplantation (HSCT) recipients (vaccine efficacy [VE] of 68.2%), patients with solid or hematopoietic malignancies (VE of 87.2%), those infected with HIV or after solid organ transplantation. The serious AEs ratio is comparable between placebo and RZV recipients (risk ratios ranged from 0.79 to 1.99) [25, 32–38].

Moreover, long-term HZ prevention in autologous HSCT has been shown, as immunogenicity was sustained up to 10 years after vaccination [39].

KIDNEY TRANSPLANT RECIPIENTS (KTRS)

Research into the efficacy and safety of recombinant adjuvanted vaccines against HZ in renal recipient populations is emerging in the literature. A phase III study investigating the safety and immunogenicity of two doses of RZV in KTRs (aged ≥ 18 years) showed humoral responses at month 2 (anti-glycoprotein E antibody geometric mean concentrations of 19163.8 mIU/mL) that persisted until month 13 (8545 mIU/mL). The antibody titers were significantly higher than pre-vaccination baseline levels and significantly higher than in the placebo group. What is more, cellular-mediated immunogenicity was measured, and the study objectives were met (vaccine response rate [VRR] in the RZV group was 80.2% at month 2). No clinically relevant safety concerns were identified as the vaccinated KTR group reported mild to moderate AEs, such as myalgia, shivering, and fever with a median duration of ≤ 4 days [34]. Another study carried out by Lindemann et. Al. showed that RZV is associated with the strongest vaccination-induced cellular immunity against the VZV gE peptide. The responses measured with interferon-gamma ELISpot after stimulation with a gE peptide after the second dose of vaccine were 8-fold and 4.8-fold higher than the response before vaccination and after the first dose, respectively [40]. Similar results regarding increased cellular and humoral responses after RZV were shown in a cross-sectional study by Roch et. Al. on 39 immunosuppressed KTRs [41].

A matter of great concern Is the potential vaccine-induced allograft rejection. In the mentioned study, no difference was observed in terms of rejection between the placebo and RZV. No biopsy-proven rejection was observed in first 30 day post-vaccination. A total of 11 rejection processes were recorded (4 in RZV, 7 in the placebo group), of which 1 was in the RZV group and 4 in the placebo group in KTRs with low rejection risk based on PRA/cPRA (PRA/cPRA, 0–19%). Allograft function was similar in both groups in long-term follow-up [34].

RZV was also shown to be safe and effective in VZV-seronegative SOT patients and may be considered as prevention against primary VZV infection [42].

There are several ongoing clinical studies investigating ZVL administered before renal transplantation.

LIVER TRANSPLANT RECIPIENTS

Herpes zoster remains a risk factor for chronic liver disease (CLD) decompensation. Although the probability of HZ occurrence in CLD patients is similar to the general population, it significantly increases after liver transplantation and as a result of the associated immunosuppression. Therefore, the Advisory Committee on Immunization Practices (ACIP) recommends vaccination against HZ in the pre-transplantation period in patients aged ≥ 50 years (RZV is preferred). As CLD severity progresses, vaccine efficacy declines, thus for optimal immune response, vaccines should be ideally administered early in the disease course. The overall incidence of HZ in liver recipients in the first year after transplantation is around 6%, increases up to 12% in 10-year follow-up, and is lower than in other SOT recipients. No HZ risk factors, attributed specifically to liver transplantation, were identified in multivariate analysis [Ref?] . Serious

complications such as visceral dissemination, cranial nerve involvement, or death are uncommon after OLT, but patients may suffer from long-lasting PHN with a significant decrease in the quality of life [43]. Vaccinations against HZ in liver recipients turned out to be safe and effective. In the post-transplantation period, ZVL vaccines are contraindicated, and RZV is the vaccine of choice [44, 45].

LUNG AND HEART TRANSPLANT RECIPIENTS

The lung and heart transplant recipient are at very high risk of *herpes zoster* and its complications. The data describing the safety and efficacy of the HZ vaccines are, however, limited. In a recently published study, the immunogenicity and safe profile of RZV in LuTx recipients (aged ≥ 50 years, > 90 days after LuTx, VZV-IgG-seropositive) was presented. There was an increase in the percentage of VZV gE-specific CD4+T cells from a median of 85 $CD4^{2+}$ T cells per 10^6 CD4 T cells (IQR: 46–180) before vaccination to a median of 361 $CD4^{2+}$ T cells per 10^6 CD4 T cells (IQR: 146–848; $p < 0.0001$) after the second dose of vaccine. During the follow-up, mostly local AEs were reported (tenderness at the injection site, redness and swelling; all were self-limiting). Several severe AEs (respiratory failures, death, and graft rejection) were observed; however, due to a long interval between AEs and RZV immunization, these episodes were classified as unrelated to vaccination [46].

The data concerning heart transplant recipients are limited. Several single-center studies have been performed; however, efficacy was not evaluated. Vaccination with RZV in HTx recipients was well tolerated. Reported AEs were mostly mild and local (arm soreness, swelling). There was no evidence of an increased allograft rejection ratio [47]. The efficacy of vaccination against HZ before transplantation was, however, suggested as a decrease in the clinical development of HZ was observed [48] [Unclear sentence].

RECOMMENDATIONS FOR THE USE OF *HERPES ZOSTER* VACCINES IN SOLID ORGAN TRANSPLANT RECIPIENTS IN POLAND

1. All adult (≥18 years of age) solid organ transplant recipients should be vaccinated against herpes zoster.
2. All adult (≥ 18 years of age) candidates qualified for organ transplantation should be vaccinated against herpes zoster before transplantation. If possible, the vaccine should be administered when the primary disease is stable. The recombinant adjuvanted vaccine is recommended.
3. The recombinant adjuvanted vaccine is recommended in the post-transplantation period. The live, attenuated VZV vaccine is contraindicated after organ transplantation.
4. Two RZV doses are necessary, regardless of previous history of herpes zoster, VZV vaccination, and VZV-IgG status.
5. In patients not vaccinated before transplantation, the first dose of RZV is recommended at least 3–6 months after transplantation. The second RZV dose should be administered 2–6 months after the first. No booster doses are recommended.
6. Currently, it is not recommended to perform serological or cellular response tests to assess response to vaccination against herpes zoster.
7. Vaccination may be administered during antiviral treatment or prophylaxis.
8. RZV can be administered concomitantly with other vaccines; however, at different anatomic sites. If possible, administration of the second vaccine should be postponed due to post-vaccination adverse events overlaps.
9. Before vaccination, providers should counsel patients about expected local and systemic adverse events. It is not recommended to take antipyretic or analgesic medications prophylactically before vaccination.
10. The only permanent contraindication to herpes zoster vaccination is hypersensitivity to any component of the vaccine or serious AEs following the previous dose.
11. Short-term prophylaxis with acyclovir or valacyclovir is recommended for organ recipients who are HSV and VZV seropositive and not receiving CMV prophylaxis.
12. If herpes zoster occurs after organ transplantation, the RZV dose should be administered at least 1 year after the incident.
13. Herpes zoster vaccines should be widely available to all patients qualified for solid organ transplantation as well as to organ recipients.

ETHICS STATEMENT:

Not required

AUTHOR CONTRIBUTIONS:

Conceptualization — ADŚ.; Writing — all authors. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST:

All authors participated in GlaxoSmithKline's expert panel: EXPERT ROUND TABLE DISCUSSION ON REDUCING THE RISK OF DEVELOPING HERPES ZOSTER INFECTION IN PATIENTS AFTER ORGAN TRANSPLANTATION AND IN POTENTIAL RECIPIENTS ON THE WAITING LIST FOR TRANSPLANTATION.

ACKNOWLEDGEMENTS

The authors thank Izabella Kuźmiuk-Glembin M.D, Ph.D. from the Department of Nephrology, Transplantology and Internal Diseases, Medical University of Gdańsk for assistance in medical writing and editorial support.

References

1. Weller TH. Varicella and herpes zoster. Changing concepts of the natural history, control, and importance of a not-so-benign virus. N Engl J Med. 1983; 309(23): 1434–1440, doi: 10.1056/NEJM198312083092306, indexed in Pubmed: 6195526.
2. Zerboni L, Sen N, Oliver SL, et al. Molecular mechanisms of varicella zoster virus pathogenesis. Nat Rev Microbiol. 2014; 12(3): 197–210, doi: 10.1038/nrmicro3215, indexed in Pubmed: 24509782.
3. Tseng HFu, Bruxvoort K, Ackerson B, et al. The Epidemiology of Herpes Zoster in Immunocompetent, Unvaccinated Adults ≥50 Years Old: Incidence, Complications, Hospitalization, Mortality, and Recurrence. J Infect Dis. 2020; 222(5): 798–806, doi: 10.1093/infdis/jiz652, indexed in Pubmed: 31830250.
4. Schmader K. Herpes Zoster. Clin Geriatr Med. 2016; 32(3): 539–553, doi: 10.1016/j.cger.2016.02.011, indexed in Pubmed: 27394022.
5. John AR, Canaday DH. Herpes Zoster in the Older Adult. Infect Dis Clin North Am. 2017; 31(4): 811–826, doi: 10.1016/j.idc.2017.07.016, indexed in Pubmed: 29079160.
6. Marra F, Parhar K, Huang B, et al. Risk Factors for Herpes Zoster Infection: A Meta-Analysis. Open Forum Infect Dis. 2020; 7(1): ofaa005, doi: 10.1093/ofid/ofaa005, indexed in Pubmed: 32010734.
7. Bhavsar A, Lonnet G, Wang C, et al. Increased Risk of Herpes Zoster in Adults ≥50 Years Old Diagnosed With COVID-19 in the United States. Open Forum Infect Dis. 2022; 9(5): ofac118, doi: 10.1093/ofid/ofac118, indexed in Pubmed: 35392454.
8. Yenikomshian MA, Guignard AP, Haguinet F, et al. The epidemiology of herpes zoster and its complications in Medicare cancer patients. BMC Infect Dis. 2015; 15: 106, doi: 10.1186/s12879-015-0810-6, indexed in Pubmed: 25888128.
9. Varicella and herpes zoster vaccines: WHO position paper, June 2014--Recommendations. Vaccine. 2016; 34(2): 198–199, doi: 10.1016/j.vaccine.2014.07.068, indexed in Pubmed: 26723191.
10. Johnson RW, Alvarez-Pasquin MJ, Bijl M, et al. Herpes zoster epidemiology, management, and disease and economic burden in Europe: a multidisciplinary perspective. Ther Adv Vaccines. 2015; 3(4): 109–120, doi: 10.1177/2051013615599151, indexed in Pubmed: 26478818.
11. Patil A, Goldust M, Wollina U. Herpes zoster: A Review of Clinical Manifestations and Management. Viruses. 2022; 14(2), doi: 10.3390/v14020192, indexed in Pubmed: 35215786.
12. Curran D, Matthews S, Boutry C, et al. Natural History of Herpes Zoster in the Placebo Groups of Three Randomized Phase III Clinical Trials. Infect Dis Ther. 2022; 11(6): 2265–2277, doi: 10.1007/s40121-022-00689-7, indexed in Pubmed: 36322332.
13. Shaikh S, Ta CN. Evaluation and management of herpes zoster ophthalmicus. Am Fam Physician. 2002; 66(9): 1723–1730, indexed in Pubmed: 12449270.
14. Bienkowski C, Kowalczyk M, Talarek E, et al. Meningitis and Ramsay-Hunt syndrome in a 17-year old girl. Neuroendocrinol Lett. 2019; 40: 149–151.
15. Albrecht P, Patrzałek M, Goryński P. Zagrożenie półpaścem i jego powikłaniami w Polsce i na świecie w zależności od wieku. Przegl Epidemiol. 2015; 69: 841–843.
16. Dworkin RH, Gnann JW, Oaklander AL, et al. Diagnosis and assessment of pain associated with herpes zoster and postherpetic neuralgia. J Pain. 2008; 9(1 Suppl 1): S37–S44, doi: 10.1016/j.jpain.2007.10.008, indexed in Pubmed: 18166464.
17. Jung BF, Johnson RW, Griffin DRJ, et al. Risk factors for postherpetic neuralgia in patients with herpes zoster. Neurology. 2004; 62(9): 1545–1551, doi: 10.1212/01.wnl.0000123261.00004.29, indexed in Pubmed: 15136679.
18. Gross GE, Eisert L, Doerr HW, et al. S2k guidelines for the diagnosis and treatment of herpes zoster and postherpetic neuralgia. J Dtsch Dermatol Ges. 2020; 18(1): 55–78, doi: 10.1111/ddg.14013, indexed in Pubmed: 31951098.
19. Parameswaran GI, Drye AF, Wattengel BA, et al. Increased Myocardial Infarction Risk Following Herpes Zoster Infection. Open Forum Infect Dis. 2023; 10(4): ofad137, doi: 10.1093/ofid/ofad137, indexed in Pubmed: 37035490.
20. Forbes HJ, Bhaskaran K, Thomas SL, et al. Quantification of risk factors for herpes zoster: population based case-control study. BMJ. 2014; 348: g2911, doi: 10.1136/bmj.g2911, indexed in Pubmed: 25134101.
21. Arvin A. Aging, immunity, and the varicella-zoster virus. N Engl J Med. 2005; 352(22): 2266–2267, doi: 10.1056/NEJMp058091, indexed in Pubmed: 15930416.
22. Pergam SA, Forsberg CW, Boeckh MJ, et al. Herpes zoster incidence in a multicenter cohort of solid organ transplant recipients. Transpl Infect Dis. 2011; 13(1): 15–23, doi: 10.1111/j.1399-3062.2010.00547.x, indexed in Pubmed: 20636480.
23. Kho MML, Roest S, Bovée DM, et al. Herpes Zoster in Solid Organ Transplantation: Incidence and Risk Factors. Front Immunol. 2021; 12: 645718, doi: 10.3389/fimmu.2021.645718, indexed in Pubmed: 33815403.
24. Kim W, Kim S, Oh J, et al. Incidence and risk factors for herpes zoster after adult liver transplantation. Ann Surg Treat Res. 2019; 96(2): 95–99, doi: 10.4174/astr.2019.96.2.95, indexed in Pubmed: 30746357.
25. Sullivan KM, Farraye FA, Winthrop KL, et al. Safety and efficacy of recombinant and live herpes zoster vaccines

for prevention in at-risk adults with chronic diseases and immunocompromising conditions. Vaccine. 2023; 41(1): 36–48, doi: 10.1016/j.vaccine.2022.10.063, indexed in Pubmed: 36460534.
26. Davis AR, Sheppard J. Herpes Zoster Ophthalmicus Review and Prevention. Eye Contact Lens. 2019; 45(5): 286–291, doi: 10.1097/ICL.0000000000000591, indexed in Pubmed: 30844951.
27. Gabutti G, Valente N, Sulcaj N, et al. Italian Universities and Epidemiology. [Herpes Zoster and its prevention in Italy. Scientific consensus statement]. Ig Sanita Pubbl. 2014; 70(1): 111–127, indexed in Pubmed: 24770367.
28. Lal H, Cunningham AL, Godeaux O, et al. ZOE-50 Study Group. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med. 2015; 372(22): 2087–2096, doi: 10.1056/NEJMoa1501184, indexed in Pubmed: 25916341.
29. Cunningham AL, Heineman TC, Lal H, et al. ZOE-50/70 Study Group, ZOE-50/70 Study Group, ZOE-70 Study Group, ZOE-50 Study Group. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med. 2015; 372(22): 2087–2096, doi: 10.1056/NEJMoa1501184, indexed in Pubmed: 25916341.
30. Kim JH, Johnson R, Kovac M, et al. Adjuvanted recombinant zoster vaccine decreases herpes zoster-associated pain and the use of pain medication across 3 randomized, placebo-controlled trials. Pain. 2023; 164(4): 741–748, doi: 10.1097/j.pain.0000000000002760, indexed in Pubmed: 36066965.
31. Chlibek R, Pauksens K, Rombo L, et al. Long-term immunogenicity and safety of an investigational herpes zoster subunit vaccine in older adults. Vaccine. 2016; 34(6): 863–868, doi: 10.1016/j.vaccine.2015.09.073, indexed in Pubmed: 26432913.
32. Duchini A, Goss JA, Karpen S, et al. Vaccinations for adult solid-organ transplant recipients: current recommendations and protocols. Clin Microbiol Rev. 2003; 16(3): 357–364, doi: 10.1128/CMR.16.3.357-364.2003, indexed in Pubmed: 12857772.
33. Kumar D. Immunizations following solid-organ transplantation. Curr Opin Infect Dis. 2014; 27(4): 329–335, doi: 10.1097/QCO.0000000000000078, indexed in Pubmed: 24945614.
34. Vink P, Ramon Torrell JM, Sanchez Fructuoso A, et al. Z-041 Study Group. Immunogenicity and Safety of the Adjuvanted Recombinant Zoster Vaccine in Chronically Immunosuppressed Adults Following Renal Transplant: A Phase 3, Randomized Clinical Trial. Clin Infect Dis. 2020; 70(2): 181–190, doi: 10.1093/cid/ciz177, indexed in Pubmed: 30843046.
35. Bastidas A, de la Serna J, El Idrissi M, et al. ZOE-HSCT Study Group Collaborators. Effect of Recombinant Zoster Vaccine on Incidence of Herpes Zoster After Autologous Stem Cell Transplantation: A Randomized Clinical Trial. JAMA. 2019; 322(2): 123–133, doi: 10.1001/jama.2019.9053, indexed in Pubmed: 31287523.
36. Dagnew AF, Ilhan O, Lee WS, et al. Zoster-039 study group. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies: a phase 3, randomised, clinical trial and post-hoc efficacy analysis. Lancet Infect Dis. 2019; 19(9): 988–1000, doi: 10.1016/S1473-3099(19)30163-X, indexed in Pubmed: 31399377.
37. Pergam SA, Limaye AP. AST Infectious Diseases Community of Practice. Varicella zoster virus in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019; 33(9): e13622, doi: 10.1111/ctr.13622, indexed in Pubmed: 31162727.
38. Anderson TC, Masters NB, Guo A, et al. Use of Recombinant Zoster Vaccine in Immunocompromised Adults Aged ≥19 Years: Recommendations of the Advisory Committee on Immunization Practices - United States, 2022. MMWR Morb Mortal Wkly Rep. 2022; 71(3): 80–84, doi: 10.15585/mmwr.mm7103a2, indexed in Pubmed: 35051134.
39. Strezova A, Diez-Domingo J, Al Shawafi K, et al. Zoster-049 Study Group. Long-term Protection Against Herpes Zoster by the Adjuvanted Recombinant Zoster Vaccine: Interim Efficacy, Immunogenicity, and Safety Results up to 10 Years After Initial Vaccination. Open Forum Infect Dis. 2022; 9(10): ofac485, doi: 10.1093/ofid/ofac485, indexed in Pubmed: 36299530.
40. Lindemann M, Baumann C, Wilde B, et al. Prospective, Longitudinal Study on Specific Cellular Immune Responses after Vaccination with an Adjuvanted, Recombinant Zoster Vaccine in Kidney Transplant Recipients. Vaccines (Basel). 2022; 10(6), doi: 10.3390/vaccines10060844, indexed in Pubmed: 35746452.
41. Roch T, Wehler P, Blazquez-Navarro A, et al. Kidney Transplant Patients Generate Varicella Zoster-Reactive T-cell and Humoral Immunity Following Protein-based Varicella Zoster Vaccination. Transplantation. 2023; 107(2): e58–e59, doi: 10.1097/TP.0000000000004406, indexed in Pubmed: 36696521.
42. L'Huillier AG, Hirzel C, Ferreira VH, et al. Evaluation of Recombinant Herpes Zoster Vaccine for Primary Immunization of Varicella-seronegative Transplant Recipients. Transplantation. 2021; 105(10): 2316–2323, doi: 10.1097/TP.0000000000003621, indexed in Pubmed: 33528118.
43. Levitsky J, Kalil A, Meza JL, et al. Herpes zoster infection after liver transplantation: a case-control study. Liver Transpl. 2005; 11(3): 320–325, doi: 10.1002/lt.20356, indexed in Pubmed: 15719387.
44. Alukal JJ, Naqvi HA, Thuluvath PJ. Vaccination in Chronic Liver Disease: An Update. J Clin Exp Hepatol. 2022; 12(3): 937–947, doi: 10.1016/j.jceh.2021.12.003, indexed in Pubmed: 34975241.
45. Dooling KL, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines. MMWR Morb Mortal Wkly Rep. 2018; 67(3): 103–108, doi: 10.15585/mmwr.mm6703a5, indexed in Pubmed: 29370152.
46. Hirzel C, L'Huillier AG, Ferreira VH, et al. Safety and immunogenicity of adjuvanted recombinant subunit herpes zoster vaccine in lung transplant recipients. Am J Transplant. 2021; 21(6): 2246–2253, doi: 10.1111/ajt.16534, indexed in Pubmed: 33565711.
47. Barghash MH, Taimur S, Rana M, et al. Recombinant herpes zoster vaccine after heart transplantation: A single-center experience. J Heart Lung Transplant. 2020; 39(12): 1501–1503, doi: 10.1016/j.healun.2020.09.001, indexed in Pubmed: 33067105.
48. Kittleson M, Patel J, Chang D, et al. Effect of the Shingles Vaccine in Altering Clinical Shingles after Heart Transplantation. The Journal of Heart and Lung Transplantation. 2020; 39(4): S479, doi: 10.1016/j.healun.2020.01.032.

REVIEW PAPER

Renal Disease and Transplantation Forum
2023, vol. 16, no. 4, 127–134

ISSN 2720–2771
e-ISSN: 2720-4189
DOI: 10.5603/rdatf.97029

Łukasz Jankowski, Julia Stępień, Zuzanna Sala, Marcin Jurczak, Magdalena Durlik

Department of Transplantology, Immunology, Nephrology and Internal Diseases, Medical University of Warsaw

The role of protocolar biopsy in the diagnosis of kidney allograft dysfunction

Abstract

Core-needle biopsy in patients with impaired renal transplant function and histopathological evaluation of the obtained tissue samples is a recognized diagnostic method of numerous graft pathologies. Until now the use of this invasive procedure in patients with no revealed signs of transplant pathology and with a stable function of the transplanted kidney at planned intervals after transplantation (the so-called protocol biopsies) has seemed inconclusive.

It is known that changes in the biopsy of the transplanted kidney are an earlier marker of transplant pathology in relation to laboratory abnormalities and the appearance of clinical symptoms, and the accumulation of subclinically progressing chronic changes is currently considered to be the main cause of renal graft loss. The histopathological evaluation also allows for the assessment of prognosis and the introduction of possible changes in the ongoing treatment. Opponents of protocol biopsy emphasize that it is an invasive procedure and exposes the patient to complications. Due to controversial reports on the usefulness of this method, protocol biopsies are not a routine tool for monitoring transplantation in transplant centers both in Poland and in the world. There is no established regimen for performing them.

This review article summarizes the current state of knowledge concerning the use of protocol biopsies in the diagnosis of transplanted kidney.

Key words: protocolar biopsy, kidney transplantation, sublinical antibody mediated rejection, subclinical T cell mediated rejection

INTRODUCTION

Extending long-term survival of the kidney graft constitutes one of the main challenges in organ transplantation. The main cause of graft loss in the long-term follow-up period is the accumulation of irreversible chronic lesions resulting from untreated or unresponsive to treatment rejection-related processes [1]. Deterioration of the graft kidney function, manifested by increased creatinine levels and decreased eGFR, is usually a late symptom of the developing pathology.

Such lesions may be detected by histopathological examination of a kidney graft specimen at a much earlier stage, which offers a chance to initiate treatment before irreversible chronic graft damage takes place. Protocol biopsy is dedicated to detecting graft pathologies at an early stage, when injury progression may still be halted**.** In the last 15 years, opinions on the diagnostic and prognostic utility of the graft kidney biopsy have varied. Following the introduction of potent immunosuppressants in the 1990s and the resulting drop in the incidence rates of acute T cell-mediated rejections (TCMR), many researchers came to believe that protocolar biopsies were unwarranted as they failed to provide information that would lead to therapeutic management modification. However, recent years have shown that graft kidney dysfunction is caused primarily by an antibody-mediated rejection (ABMR) process and is associated with the *de novo* production of donor-specific antibodies (DSA) at any time after transplantation [2]. The rejection may be clinically silent. The findings have shed light on potential utility of protocol biopsy as a tool for detecting clinically silent pathologies at a stage where progression can still be halted. A wealth of information was provided in the 2015 publication, in which Loupy et al. presented the results of 1001 protocol biopsies, performed 12 months after kidney trans-

Address for correspondence:
lek. Łukasz Jankowski
Department of Transplantology, Immunology, Nephrology and Internal Diseases, Medical University of Warsaw
ul. Nowogrodzka 59,
02-006 Warszawa
tel.: (22) 502 12 32
e-mail: lkszjankowski@gmail.com

plantation (KTx), which revealed subclinical T cell-mediated rejection in 13% and subclinical ABMR in 14% of cases. In the further 8-year follow-up period, patients with subclinical ABMR had significantly worse graft survival (56%) compared with patients with subclinical TCMR (88%) and patients without rejection (90%) ($p < 0.001$). In a multivariate analysis, subclinical ABMR one year after KTx was associated with a 3.5-fold increase in graft loss, decrease in eGFR and proteinuria. As for patients with subclinical TCMR one year after KTx, only those who had developed DSAs and graft glomerulopathy had a higher risk of graft loss, compared with patients without rejection. According to the Authors, subclinical ABMR and TCRM affect graft survival in a different way. Subclinical ABMR was a risk factor for graft function deterioration and loss regardless of baseline DSAs status, eGFR and proteinuria. Subclinical T cell-mediated rejection did not lead to graft function deterioration but increased de novo production of DSAs [3].

The publications available focused also on identifying specific groups of patients who might require intensive histopathological surveillance and would benefit from protocol biopsy as a sensitive diagnostic tool [4]. Despite its likely benefits, protocol biopsy is rarely used to monitor the graft kidney function, either in Poland or worldwide. According to UNOS (United Network for Organ Sharing) survey from 88 transplant centers in US forty percent (n = 36) centers reported performing protocol biopsies (20% in all cases and 20% in select cases). The most common time points for performing protocol biopsies were 3- and 12-months (72% each), 6-months (44%), 1-month (31%), and 24-months (25%). Two centers reported performing them at 60 months post transplantation. For diagnosing TCMR, 100% used indication biopsy, 28% used protocol biopsy, 2% used serum biomarkers, and none used urine cytokines. For ABMR, 99% used indication biopsy, 34% used protocol biopsy, 72% used DSA, 21% used C1q positive DSA, and none used gene profiling [5].

TECHNIQUE AND SAFETY OF THE PROCEDURE

The procedure is carried out by nephrologists or surgeons, and occasionally by other specialists. Given the non-anatomical location of the transplanted kidney, most centres perform an ultrasound scan immediately before the procedure to accurately assess the graft topography and rule out possible contraindications to the procedure. In patients receiving an anticoagulant or antiplatelet therapy, protocol biopsy may usually be planned in advance or such therapy may be discontinued and, if the patient's condition so requires, low molecular weight heparin may be administered temporarily, which may then be discontinued immediately before the procedure [6].

The most common complications of graft kidney biopsy include perirenal haematomas, while intrarenal arteriovenous fistulas are a little less common. The estimated incidence rates of graft kidney biopsy complications requiring therapeutic management, e.g. blood transfusion or surgical intervention, range from 0% to 4% according to different authors, however, protocolar biopsy is associated with an up to 10-fold lower risk of complications compared with biopsy performed "when indicated" [7]. This is related to the planned preparation for the procedure, as well as the patient's good condition at baseline (usually). Taking into account the data available, the prevailing opinion is that protocolar biopsy of the graft kidney is a safe procedure, associataed with only a low risk of complications, and may be offered to kidney transplant recipients as a routine diagnostic procedure [8].

PRACTICAL UTILITY OF PROTOCOLAR BIOPSIES

Protocolar biopsies are performed at fixed intervals, and the exact schedule depends on the centre's experience and clinical situation. Typically, the first protocolar biopsy is performed on the operating table, during the transplantation procedure, immediately after organ reperfusion. Some authors even propose biopsy "0" (the so-called implantation biopsy), immediately after transplantation, and the so-called biopsy "1 hour," performed one hour after reperfusion, which is supposed to allow for a more accurate assessment of the graft kidney baseline status and the prognosis, taking into account possible early immune reactions and reperfusion-related damage. Such biopsy, in addition to baseline graft assessment, may offer some prognostic information — it has been demonstrated that detection of interstitial fibrosis with tubular atrophy (IF/TA) in specimens collected in the first hours after organ implantation constitutes a negative

prognostic factor and is associated with lower eGFR of the graft [9]. Similarly, the presence of IF/TA, particularly in combination with features of chronic inflammation identified by subsequent biopsies, also constitues an unfavourable prognostic factor for graft survival. Clearly, the time points may be affected by the patient's individual clinical situation, including the baseline donor-recipient immunological risk status, immunosuppressive and induction therapy, further plans, e.g. minimisation of immunosuppression (IS), and chronically elevated serum levels of calcineurin inhibitors [10]. In general, it is thought that earlier protocolar biopsies are associated with a greater chance of detecting subclinical alloimmune responses (which usually develop within the first three months of transplantation; such biopsy may provide important data that may affect decisions on further IS treatment and possibly minimization of IS), while 1-year biopsies offer a greater chance of detecting graft pathologies such as BK virus infection, recurrence of the underlying disease (glomerulonephritis), lesions resulting from nephrotoxicity of calcineurin inhibitors or signs of chronic inflammation, which has a prognostic value. Subsequently 3-, 5-, 7-, and even 10-year biopsies can be performed to evaluate chronic ABMR, the main cause of graft loss. Annual DSA monitoring is strongly recommended for all kidney transplant recipients. TCMR usually disappeares by the 3-year biopsy. Based on detecting pathological changes from protocol biopsy there is possibility of changing diagnosis, changing treatment, reducing immunosuppression dose [11, 12].

Protocol biopsies may be a useful tool to detect viral infections such as BKVN because early diagnosis is necessary to resolve infection and prevent chronic damage. Buehrig et al. demonstrated that all patients with BKVN diagnosed by protocol biopsies and managed by immunosuppression reduction had a satisfactory outcome by 6 months after diagnosis; in contrast, 70% of those with a late diagnosis by indication biopsies had deterioration of kidney function or graft loss. Since many reports support the utility BK virus DNA PCR as a screening strategy for BKVN, protocol biopsies only for BKVN may be unnecessary [13].

Recurrence of native kidney disease following kidney transplantation affects between 10% and 20% of patients, and accounts for up to 8% of graft failures at 10 years post transplant. Subclinical recurrence of both primary and secondary glomerular diseases is well recognized. Asymptomatic histological recurrence in renal allografts may be missed if protocol biopsies are not available. However the histological diagnosis may be missing because many transplant biopsies are not routinely processed using immunofluorescence and electron microscopy. Another limitations of utility of protocol biopsy for diagnosis of recurrent glomerulonephritis include unknown cause of native kidney disease, donor transmitted glomerulonephritis, lack of histologic features of FSGS in early stage of recurrence. Recurrence of glomerulonephritis in majority of patients is diagnosed in biopsy for cause due to proteinuria [14].

It should be emphasised that both T cell-mediated rejection and antibody-mediated rejection may have subclinical presentation. Early initiation of treatment of these pathologies allows to prevent progression of the lesions as well as the development of IF/TA or chronic graft glomerulopathy, thereby extending graft survival. One cannot omit the psychological aspect of the surveillance biopsies in graft recipients – when presented with the current state of knowledge of graft kidney protocolar biopsy and the benefits associated with the procedure, as well as the risks associated with this invasive procedure, few patients refuse to consent to biopsy and inclusion in the protocolar biopsy programme. This is all the more noteworthy as protocolar biopsy is associated with hospitalisation at the primary centre, which on the one hand constitutes an inconvenience, especially that protocolar biopsy is not performed because of any indications, but on the other — means an opportunity of medical surveillance in the inpatient settings.

It is important to dispel doubts about the eligibility of specific patient groups to protocolar biopsy. There have been reports on groups of patients in whom protocolar biopsies do not provide significant benefits with respect to the risk associated with the procedure. Biopsies performed within the first two weeks of transplantation appear to be of no benefit to low-risk patients in whom immunosuppression protocols with induction are used and who subsequently receive calcineurin inhibitors, even if delayed graft function (DGF) is the indirect indication for such a procedure [15]. This is supported by the predomiant opinion that this invasive procedure is not necessary in the case of patients with low immunological risk. Many of the publications available em-

phasise the need for individualised assessment of eligibility to biopsy, taking into account not only the immunological factors concerning the donor-recipient relationship but also the clinical profile of the recipient. Factors that should be taken into account in the eligibility assessment include the patient's age, cardiovascular diseases (heart failure before/after transplantation, atherosclerosis), type 2 diabetes mellitus, post-transplant urinary tract infections, serious infections, rejection episodes and cancer [16]. In each case, the decision to propose protocolar biopsy to a patient should be made on a case-by-case basis, taking into account a wide range of factors as well as the centre's experience in this area.

RECENT LITERATURE REVIEW

Researchers from Taiwan analysed the results of protocolar biopsies in 68 kidney recipients and compared them with the results of biopsies in 122 stable recipients two years after transplantation. The rejection process was identified by 13 protocolar biopsies, and in 11 cases borderline lesions were detected. Patients were administered glucocorticoid pulses. Over the 5-year follow-up period, graft survival was better in the protocolar biopsy group ($p = 0.0143$). In four and 17 recipients in the protocolar biopsy group and non-protocolar biopsy group, respectively, a biopsy performed because of indications confirmed the rejection process. In the recipients with the rejection process detected, the graft function was better in the protocolar biopsy group compared with the non-biopsy group. However, no difference in graft survival were observed in the 12-year follow-up period. In addition, in nine protocolar biopsies different types of glomerulopathy were identified, the most common (in four cases) being IgA glomerulopathy. No patient lost the graft because of GN. The Authors conclude that protocolar biopsy allows to detect subclinical rejection, and early intervention increase 5-year graft survival rates [17].

In a retrospective study, French researchers from Grenoble assessed the role of protocolar biopsy performed in 333 kidney transplant recipients in 2007–2013; 282 subjects had not undergone kidney biopsy, they constituted the control group. In patients who had undergone a kidney biopsy, 5-year graft survival rates were better regardless of the patient survival rates ($p < 0.001$), compared with patients who had not undergone protocolar biopsy. As for graft kidney specimens, 212 (64%) were normal, 87 (26%) showed IF/TA of varying grade and 24 (7%) showed features of subclinical rejection, including borderline lesions in 20; the patients were effectively treated with GS pulses. Nine biopsies revealed: recurrence or de novo GN in five patients, BKV nephropathy in two patients, acute CNI nephrotoxicity in one patient and features of pyelonephritis in one patient. Among patients who had undergone biopsy, 87 (26%) had IF/TA score of > 0, and recipients with IF/TA score of 3 had the worst graft survival rates. One hundred and forty-four patients (44%) presented cv lesions (*fibrosis endarteritis*); cv2 and cv3 lesions were associated with the worst 5-year graft survival rates. According to the Authors, protocolar biopsy performed at three months improves graft survival rates, primarily thanks to early treatment of immune-mediated lesions [18].

Korean authors assessed safety and feasibility of protocolar biopsy two weeks and twelve months after KTx. In 2012–2019, 842 protocolar biopsies were performed two weeks after KTx and 399 biopsies – one year after KTx. Biopsies were technically successful and safe; the complication rates were 0.3% in the case of biopsies performed two weeks and 0.2% in the case of biopsies performed twelve months after KTx. The incidence rates of subclinical rejection were 15.4% (130/842) and 33.6% (134/399) for biopsied performed two weeks and twelve months after KTx, respectively ($p < 0.001$). The authors do not provide long-term results but emphasise that protocolar biopsy is safe and can detect the subclinical rejection process (19).

The authors from Malaysia evaluated protocolar biopsies performed in 147 recipients (334 biopsies were performed between one month and 22 years after KTx, each recipient had undergone 1–7 biopsies) between 2012 and 2017. No rejection was detected in 161 (48.2%) cases, borderline lesions were found in 145 (43.4%) cases, and subclinical rejection — in 28 (8.4%) cases. Immune-mediated lesions were more common in the first five years after KTx. Borderline lesions were identified in 59 (36.4%), 64 (54.2%) and 22 (40.7%) biopsies at < 1 year, 1–5 years and > 5 years, respectively ($p = 0.011$). Subclinical rejection was found in six (3.7%) biopsies at < 1 year, 18 (15.3%) biopsies in the period of 1–5 years and four (7.4%) biopsies at > 5 years after KTx ($p = 0.003$). IF/TA, *de novo* or recur-

rent glomerulopathy and other unexpected lesions were found in 40 (12%), 10 (3%) and 12 (3.6%) biopsies, respectively. Recipients of kidney transplants from living donors had significantly lower rates of subclinical rejection ($p = 0.007$). The authors emphasised that in spite of stable graft function, morphological examination relatively frequently revealed subclinical rejection [20].

Another publication from Spain concerns the analysis of protocolar biopsies performed 4–6 months and 12 months after KTx, in 2015–2021; 134 biopsies were performed in 100 patients — 71 biopsies 4–6 months and 63 biopsies 12 months after KTx. The biopsies revealed 19 (14%) cases of subclinical rejection and 10 (7.4%) cases of borderline lesions. In addition, nephrocalcinosis was reported in 4.4% patients, IgA nephropathy in 2.2% patients and BK virus nephropathy in 1.5% patients. Protocolar biopsy findings lead to a therapeutic intervention in 45 patients (in 33% of all biopsies), most commonly the administration of methylprednisolone pulses (12.6%) and conversion to mTOR inhibitors (8.9%). In the Authors' opinion, protocolar biopsy is a useful tool for graft function monitoring as well as early detection and treatment of subclinical lesions [21].

Mareena S. Zachariah et al. presented 5-year results of 261 protocolar biopsies in 159 kidney recipients (2004–2012), performed 3–9 months (early) and subsequently 12–24 months (late) after KTx. The morphological image was classified as: IF/TA (interstitial fibrosis/tubular atrophy), subclinical acute rejection with IF/TA and border lesions with IF/TA. The effect of these lesions on glomerular filtration rate (eGFR) was assessed with respect to eGFR 12 months after KTx. In early biopsies, normal kidney was found in 105 (66%) recipients while in the remaining 54 (34%) subjects the following pathologies were identified: subclinical acute rejection plus IF/TA in seven recipients (4.4%), borderline lesions plus IF/TA in 17 (10.69%) recipients and IF/TA in 30 (18.87%) recipients. Late biopsies were performed in 102 recipients — in 59 (58%) no pathology was identified while in 43 (42%), the findings were as follows: subclinical acute rejection plus IF/TA in four (4%) recipients, borderline lesions plus IF/TA in 8 (9%) recipients and IF/TA in 30 (29%) recipients. Glomerular filtration rate at 12 months was related to eGFR at three months, the donor's age, delayed graft function and early protocolar biopsy findings. Changes in eGFR over time were associated with IF/TA in early biopsies and subclinical rejection and borderline lesions in late biopsies. In the long-term follow-up, the final eGFR values were related to IF/TA in early biopsies and subclinical rejection in late biopsies. Early protocolar biopsies allowed to predict eGFR at 12 months, while late biopsies — graft function over time. The presence of borderline lesions in the protocolar biopsy was predictive of long-term graft function [22].

Observational study from Author's transplant centre included 61 patients who underwent protocol biopsy 12 months after the transplantation. The biopsy results revealed abnormal histologic material in 37 patients (60%), mild inflammatory lesions in 21 patients, interstitial fibrosis and tubular atrophy (IFTA) grade II to III in 12 and BK virus nephropathy in 4. Immunosuppressive treatment was modified in the group with mild inflammatory changes and in the BKV group after the biopsy result. In the group with mild inflammatory lesions, renal function was stable during 5-years follow-up. In the BKV nephropathy group, there was a significant reduction in serum creatine levels. Protocol biopsies are useful for detecting early pathologies and preventing allograft failure. Patients with detectable pathology that can be treated or in whom therapy modification is possible will benefit from protocol biopsies [23].

Naumnik et al. from another polish transplant center reported results of a prospective observational study involving seventeen kidney recipients transplanted who underwent "zero", 3-month and 12-month allograft biopsies as well as DSA assessment. Histologic analysis of the biopsies showed subclinical acute cellular rejection in 17.6% of patients at 3-months post transplantation, and additional case of borderline rejection at the 12-month point. Moreover, two cases (11.8%) of polyomavirus BK nephropathy were diagnosed (one at 3 and one at 12 month point). None of the patients developed de novo DSA. Protocol biopsies allowed Authors' to detect significant proportion of patients with subclinical, but histologically relevant acute cellular rejection and BK nephropathy. Early therapeutic intervention had beneficial effects in a 4-year follow up [24].

The Authors from Korea evaluated the 504 patients who underwent protocolar biopsies and 350 who did not undergo protocolar biopsy.

Biopsies were performed 2 weeks and one year after transplantation, 207 recipients underwent single biopsy and 297 recipients the double biopsy. The double protocol biopsy group had advantages in 5-year graft survival, CKD progression, and new-onset CKD. Authors conclude, that protocol biopsy can play a protective role in the maintenance of kidney grafts in kidney transplant recipients [25].

Mehta et al. evaluated the long-term impact of early subclinical inflammation through surveillance biopsy in a prospective observational cohort of 586 patients who underwent protocol biopsy in their first year post-transplant. Patients were classified based on their biopsy findings: 282 with no significant inflammation and 304 with subclinical inflammation and tubulitis (182 with subclinical borderline changes and 122 with subclinical T Cell mediated rejection). Adjusted odds of having a subsequent clinical biopsy proven acute rejection and death-censored graft loss were significantly higher in the subclinical inflammation group compared to no subclinical inflammation during 5-year follow-up. Overall, Authors highlighted the need for identifying patients with subclinical inflammation through surveillance biopsy and develop strategies to prevent further alloimmune injuries [26].

De novo donor-specific antibodies (dnDSAs) are associated with the development of ABMR and graft loss. A multicentre (nine centres) French study retrospectively assessed whether or not regular monitoring for *de novo* DSAs combined with biopsy should become a routine practice. In patients with *de novo* DSAs (MFI > 1000) and stable kidney function biopsies were performed. Biopsies were performed in 123 patients, on average 65.3 (median) months after KTx. Renal function had remained stable for the three preceding months. Subclinical ABMR was found in 51 (41.4%) patients, including 32 (26%) cases of active ABMR and 19 (15.5%) cases of chronic active subclinical ABMR. No ABMR was identified in 72 biopsies (58.5%). The predictors for active subclinical ABMR were as follows: dominant DSAs MFI > 4,000; MFI of the sum of DSAs > 6300, recipient's age < 45 years, and no use of GS at the time of biopsy. Proteinuria of > 200 mg/g was a predictor of chronic active subclinical ABMR. Patients with active ABMR had greater declines in GFR within five years of biopsy and worse graft survival. Biopsy in patients with *de novo* DSAs allowed to detect ABMR in 40% of cases, but the Authors did not see any improvement after treatment [27].

Early diagnosis and treatment of subclinical ABMR based on the donor-specific antibody (DSA) testing may result in better outcomes. Filippone and Faber reviewed the literature on subclinical antibody-mediated rejection (ABMR) associated with donor specific antibodies. Subclinical ABMR occurs in up to 40% of patients transplanted with preexisting DSA routinely having biopsies within the first year following transplantation and subclinical ABMR occurs in up to 40% of patients with dnDSA if biopsied by protocol at the time of initial dnDSA detection. Subclinical AMR portends adverse outcomes (worse kidney function and graft loss) whether associated with preexisting DSA or dnDSA. They recommend to perform protocol biopsies within the first year following transplantation in all patients transplanted with preexisting DSA and in all patients with dnDSA at initial detection [28].

Recently published by ESOT Working Group on Subclinical DSA Monitoring "The Clinical Utility of Post-Transplant Monitoring of Donor-Specific Antibodies in Stable Renal Transplant Recipients: A Consensus Report With Guideline Statements for Clinical Practice" recommends a routine antibody monitoring at three to six months post-transplant and annually thereafter. Monitoring for dnDSA during functional graft life is a continuous process and should not change upon detection of dnDSA [29].

All the publications presented concern retrospective observational studies, often single-centre studies, involving various study populations and biopsies performed at different post-transplantation time points; also objectives were different; however, they show that protocolar biopsies can detect subclinical rejection or borderline lesions, which may have a beneficial effect on the preservation of good graft function. Early diagnosis of subclinical antibody-mediated rejection has an additional prognostic value, although no effective therapies for this pathology are available today. Large prospective studies are necessary to fully assess the utility of protocolar biopsy.

SUMMARY

Protocol biopsy of the graft kidney is a safe diagnostic tool serving to detect pathologies at an early stage. No doubt, the introduc-

tion of protocol biopsy into clinical practice has also allowed to broaden our the knowledge of the pathophysiology of the graft kidney lesions. However, at present, the role of protocol biopsy as a routine diagnostic tool is still under discussion, therefore it is not performed in all centres. Based on the experience gained so far, it seems possible to limit this examination to the groups of patients who would derive the greatest clinical benefit. Such groups would include primarily patients with an increased risk of rejection, higher sensitisation degree and after incompatible transplantation (immunologic or blood type incompatibilities), as well as patients in whom IS minimisation protocols are used, with lower doses of calcineurin inhibitors or steroids. However, this requires further analyses. Certainly, the decision to provide surveillance via protocol biopsy should always be made on a case-by-case basis, taking into account not only immunological but also clinical factors, as well as the centre's experience. With time and with the development of the immunosuppressants segment and noninvasive diagnostic techniques, the role of graft kidney biopsy, including protocol biopsy, will decrease. There have already been reports of non-invasive tests with similar sensitivity and specificity in diagnosing graft rejection. However, their introduction into routine clinical practice will require time and further testing. Noninvasive biomarkers include urine chemokines, TTV replication, gene profiling, proteomics and dd cf DNA. The latter seems to be the most promising biomarker and currently commercially available in some countries [30, 31].

AUTHOR CONTRIBUTIONS

Łukasz Jankowski — research concept and design, collection and/or assembly of data, data analysis and interpretation, writing the article, critical revision of the article, final approval of the article;
Julia Stępień — writing the article, final approval of the article;
Marcin Jurczak — writing the article, final approval of the article;
Zuzanna Sala — writing the article, final approval of the article;
Magdalena Durlik — critical revision of the article, final approval of the article.

FUNDING

None.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

References

1. Ndemera H, Bhengu B. Factors Contributing to Kidney Allograft Loss and Associated Consequences among Post Kidney Transplantation Patients. Health Science Journal. 2017; 11(3), doi: 10.21767/1791-809x.1000504.
2. Sellarés J, de Freitas DG, Mengel M, et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. Am J Transplant. 2012; 12(2): 388–399, doi: 10.1111/j.1600-6143.2011.03840.x, indexed in Pubmed: 22081892.
3. Loupy A, Vernerey D, Tinel C, et al. Subclinical Rejection Phenotypes at 1 Year Post-Transplant and Outcome of Kidney Allografts. J Am Soc Nephrol. 2015; 26(7): 1721–1731, doi: 10.1681/ASN.2014040399, indexed in Pubmed: 25556173.
4. Pani A, regorini M, Rampino T, et al. L'utilita' delle biopsie protocollari nel trapianto di rene: pro e contro [The usefulness of protocol biopsies after kidney transplant: pros and cons]. G Ital Nefrol. 2010; 27: 339–352.
5. Sood P, Cherikh WS, Toll AE, et al. Kidney allograft rejection: Diagnosis and treatment practices in USA-A UNOS survey. Clin Transplant. 2021; 35(4): e14225, doi: 10.1111/ctr.14225, indexed in Pubmed: 33455009.
6. Chapman JR. Do protocol transplant biopsies improve kidney transplant outcomes? Curr Opin Nephrol Hypertens. 2012; 21(6): 580–586, doi: 10.1097/MNH.0b013e32835903f4, indexed in Pubmed: 23042026.
7. Morgan TA, Chandran S, et al. Complications of Ultrasound-Guided Renal Transplant Biopsies. Am J Transplant. 2016: 1298–1305, doi: 10.1111/ajt.13622, indexed in Pubmed: 26601796.
8. Furness PN, Philpott CM, Chorbadjian MT, et al. Protocol biopsy of the stable renal transplant: a multicenter study of methods and complication rates. Transplantation. 2003; 76(6): 969–973, doi: 10.1097/01.TP.0000082542.99416.11, indexed in Pubmed: 14508363.
9. Fahmy LM, Massie AB, Muzaale AD, et al. Long-term Renal Function in Living Kidney Donors Who Had Histological Abnormalities at Donation. Transplantation. 2016; 100(6): 1294–1298, doi: 10.1097/TP.0000000000001236, indexed in Pubmed: 27152920.
10. Huang Y, Farkash E. Protocol Biopsies: Utility and Limitations. Adv Chronic Kidney Dis. 2016; 23(5): 326–331, doi: 10.1053/j.ackd.2016.09.002, indexed in Pubmed: 27742388.
11. Sakai K, Oguchi H, Muramatsu M, et al. Protocol graft biopsy in kidney transplantation. Nephrology (Carlton). 2018; 23 Suppl 2: 38–44, doi: 10.1111/nep.13282, indexed in Pubmed: 29968403.
12. Tanabe T. The value of long-term protocol biopsies after kidney transplantation. Nephrology (Carlton). 2014; 19 Suppl 3: 2–5, doi: 10.1111/nep.12253, indexed in Pubmed: 24842813.
13. Buehrig CK, Lager DJ, Stegall MD, et al. Influence of surveillance renal allograft biopsy on diagnosis and prognosis of polyomavirus-associated nephropathy. Kidney Int. 2003; 64(2): 665–673, doi: 10.1046/j.1523-1755.2003.00103.x, indexed in Pubmed: 12846764.

14. Morozumi K, Takeda A, Otsuka Y, et al. Recurrent glomerular disease after kidney transplantation: an update of selected areas and the impact of protocol biopsy. Nephrology (Carlton). 2014; 19 Suppl 3: 6–10, doi: 10.1111/nep.12255, indexed in Pubmed: 24842814.
15. Abeling T, Scheffner I, Karch A, et al. Risk factors for death in kidney transplant patients: analysis from a large protocol biopsy registry. Nephrol Dial Transplant. 2019; 34(7): 1171–1181, doi: 10.1093/ndt/gfy131, indexed in Pubmed: 29860340.
16. Favi E, James A, Puliatti C, et al. Utility and safety of early allograft biopsy in adult deceased donor kidney transplant recipients. Clin Exp Nephrol. 2020; 24(4): 356–368, doi: 10.1007/s10157-019-01821-7, indexed in Pubmed: 31768863.
17. Chen CC, Lin WC, Lee CY, et al. Two-year protocol biopsy after kidney transplantation in clinically stable recipients - a retrospective study. Transpl Int. 2021; 34(1): 185–193, doi: 10.1111/tri.13785, indexed in Pubmed: 33152140.
18. Terrec F, Noble J, Naciri-Bennani H, et al. Protocol Biopsies on de novo Renal-Transplants at 3 Months after Surgery: Impact on 5-Year Transplant Survival. J Clin Med. 2021; 10(16), doi: 10.3390/jcm10163635, indexed in Pubmed: 34441931.
19. Lim M, Park BK, Lee KW, et al. Two-Week Protocol Biopsy in Renal Allograft: Feasibility, Safety, and Outcomes. J Clin Med. 2022; 11(3), doi: 10.3390/jcm11030785, indexed in Pubmed: 35160237.
20. Fu MS, Lim SJ, Jalalonmuhali M, et al. Clinical Significance of Renal Allograft Protocol Biopsies: A Single Tertiary Center Experience in Malaysia. J Transplant. 2019; 2019: 9153875, doi: 10.1155/2019/9153875, indexed in Pubmed: 31186948.
21. Santana Quintana CA, Gallego Samper R, Santana Estupiñán R, et al. Experience and Utility of the Protocol Kidney Biopsy in the First Year of Kidney Transplantation. Transplant Proc. 2022; 54(9): 2443–2445, doi: 10.1016/j.transproceed.2022.10.008, indexed in Pubmed: 36328815.
22. Zachariah MS, Dwivedi AK, Yip CS, et al. Utility of Serial Protocol Biopsies Performed After 1 Year in Predicting Long-Term Kidney Allograft Function According to Histologic Phenotype. Exp Clin Transplant. 2018; 16(4): 391–400, doi: 10.6002/ect.2016.0323, indexed in Pubmed: 29206090.
23. Cieślik A, Burban A, Gniewkiewicz M, et al. The Importance of 1-Year Protocol Biopsy in the Long-Term Prognosis of Kidney Transplants-5-Years Follow-Up. Transplant Proc. 2023; 55(9): 2053–2057, doi: 10.1016/j.transproceed.2023.08.022, indexed in Pubmed: 37778932.
24. Naumnik B, Kowalewska J, Hryszko T, et al. Single center experience of subclinical rejections and BK nephropathies by kidney allografts' surveillance biopsies. Adv Med Sci. 2017; 62(1): 110–115, doi: 10.1016/j.advms.2016.07.005, indexed in Pubmed: 28242482.
25. Lee O, Kim MJ, Lee JE, et al. The Protective Role of Protocol Biopsy for Allograft Kidney Maintenance in Kidney Transplantation. Transplant Proc. 2023; 55(4): 756–768, doi: 10.1016/j.transproceed.2023.01.029, indexed in Pubmed: 36990887.
26. Mehta RB, Melgarejo I, Viswanathan V, et al. Long-term immunological outcomes of early subclinical inflammation on surveillance kidney allograft biopsies. Kidney Int. 2022; 102(6): 1371–1381, doi: 10.1016/j.kint.2022.07.030, indexed in Pubmed: 36049641.
27. Bertrand D, Gatault P, Jauréguy M, et al. Protocol Biopsies in Patients With Subclinical De Novo Donor-specific Antibodies After Kidney Transplantation: A Multicentric Study. Transplantation. 2020; 104(8): 1726–1737, doi: 10.1097/TP.0000000000003055, indexed in Pubmed: 32732853.
28. Filippone EJ, Farber JL. The Problem of Subclinical Antibody-mediated Rejection in Kidney Transplantation. Transplantation. 2021; 105(6): 1176–1187, doi: 10.1097/TP.0000000000003543, indexed in Pubmed: 33196628.
29. van den Broek DAJ, Meziyerh S, Budde K, et al. ESOT Working Group Subclinical DSA Monitoring. The Clinical Utility of Post-Transplant Monitoring of Donor-Specific Antibodies in Stable Renal Transplant Recipients: A Consensus Report With Guideline Statements for Clinical Practice. Transpl Int. 2023; 36: 11321, doi: 10.3389/ti.2023.11321, indexed in Pubmed: 37560072.
30. Nolan N, Valdivieso K, Mani R, et al. Clinical and Analytical Validation of a Novel Urine-Based Test for the Detection of Allograft Rejection in Renal Transplant Patients. J Clin Med. 2020; 9(8), doi: 10.3390/jcm9082325, indexed in Pubmed: 32707779.
31. Martuszewski A, Paluszkiewicz P, Król M, et al. Donor-Derived Cell-Free DNA in Kidney Transplantation as a Potential Rejection Biomarker: A Systematic Literature Review. J Clin Med. 2021; 10(2), doi: 10.3390/jcm10020193, indexed in Pubmed: 33430458.

Renal Disease and Transplantation Forum
2023, vol. 16, no. 3, 135–141

ISSN 2720–2771
e-ISSN: 2720-4189
DOI: 10.5603/rdtf.96925

Łukasz Izbiński[1], Maja Nowicka[2], Dominik Łacina[2], Viachaslau Svirydau[1], Ilona Kurnatowska[2]

[1]Department of Nephrology, Norbert Barlicki Memorial Teaching Hospital No. 1, 90-153 Lodz, Poland.
[2]Department of Internal Medicine and Transplant Nephrology, Chair of Pulmonology, Rheumatology and Clinical Immunology, Medical University of Łódź

Acute kidney injury during DRESS syndrome: a case report and literature review

Abstract

The article presents a case of a 46-year-old woman hospitalized in the Nephrology Department due to acute kidney injury with concomitant cutaneous manifestations. The patient had a history of deep vein thrombosis, resulting in intestinal resection and ileostomy 6 months before the hospitalization. On admission, the patient presented a widespread erythematous and papular eruption with pruritus, burning sensation, and scaling, involving her whole body and most pronounced on her face. The laboratory tests showed increased levels of liver and cardiac injury markers, as well as kidney dysfunction requiring temporary hemodialysis. A skin biopsy revealed chronic inflammation with abundant eosinophils. Based on these findings, the patient was diagnosed with drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, likely induced by allopurinol. The article highlights the significance of prompt identification of clinical DRESS features, the variety of which can hinder timely diagnosis and management.

Key word: drug hypersensitivity syndrome, allopurinol/adverse effects, acute kidney injury/etiology, skin diseases/etiology

INTRODUCTION

DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms) is a rare, systemic drug reaction with a severe clinical course accompanied by peripheral blood eosinophilia. The number of new cases is estimated at about 2/100,000 per year [1] with a slight predominance in women (ratio 5/4) [2]. The incidence of the syndrome varies between 0.01 and 0.1% of cases of exposure, depending on the drug used [3]. The symptoms of the syndrome occur with a delay, typically from 2 to 6 weeks after exposure to the causative agent (drug) [4] and may persist even after its discontinuation. In most cases, initially nonspecific general symptoms appear such as weakness, fever (38–40°C), skin itching and lymphadenopathy. Later, skin changes are observed: extensive maculopapular rash with subsequent scaling and erythroderma. In the course of the disease, internal organs may be involved, most often the liver, kidneys, lungs and heart. The varied clinical course makes diagnosis difficult and delays the initiation of proper treatment [5]. Nowadays, the scale according to RegiSCAR (European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples) (Tab. 1) [2, 5] is most commonly used to assess the probability of clinical DRESS. The offending agent can be identified in about 80% of cases, and in about 20% it remains unknown. The vast majority (75%) of cases are observed after exposure to a small group of drugs: allopurinol, aromatic antiepileptic drugs, sulfonamides, vancomycin, minocycline, as well as anti-tuberculosis antibiotics: rifampicin, isoniazid and ethambutol [5]. Sporadically, DRESS syndrome has also been reported after exposure to some non-steroidal anti-inflammatory drugs (ibuprofen, celecoxib), beta-lactam antibiotics (amoxicillin, piperacillin), kinase inhibitors (imatinib), antiviral drugs, omeprazole [4–6]. Kidney involvement (interstitial nephritis) occurs in 10–30% of patients; it is particularly characteristic of DRESS induced by allopurinol and may manifest in many ways from isolated proteinuria to acute kidney injury (AKI) requiring temporary or chronic renal replacement therapy (3%)

Address for correspondence:
Ilona Kurnatowska,
Department of Internal Medicine and Transplant Nephrology,
Chair of Pulmonology, Rheumatology and Clinical Immunology,
Medical University of Łódź,
90-153 Łódź, Kopcińskiego 22, Poland,
e-mail: Ilona.kurnatowska@umed.lodz.pl

Table 1. Criteria for diagnosing DRESS syndrome: < 2 — excluded, 2–3 — possible, 4–5 — probable, > 5 — definite according to RegiSCAR (European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples) and symptoms present in the presented case

Clinical parameters	No	Yes	Unknown	Presented case
Fever ≥ 101.3°F (38.5°C)	–1	0	–1	0
Lymphadenopathy	0	1	0	0
Atypical lymphocytes	0	1	0	0
Eosinophilia				
700–1499 cells/μL or 10–19,9%	0	1	0	1
≥ 1500 cells/μL or ≥ 20%	0	2	0	0
Skin rash				
Rash suggestive of DRESS (Suggestive features: ≥ 2 facial edemas, purpura, infiltration, desquamation)	-1	1	0	1
Extent ≥ 50% of BSA	0	1	0	1
Skin biopsy suggestive of DRESS	–1	0	0	0
OOrgan involvement (1 point for each organ involvement, maximum score: 2)				
1	0	1	0	1
2	0	2	0	0
Disease duration ≥ 15 days	–1	0	–1	0
Exclusion of other causes (1 point if 3 of the following tests are performed and are negative: HAV, HBV, HCV, mycoplasma, chlamydia, ANA, blood culture)	0	1	0	1
Total score				5

and occurring in about 8% of patients. AKI is defined according to the KDIGO guidelines as an increase in serum creatinine concentration by ≥ 0.3 mg/dL (26.5 μmol/L) within 48 hours or ≥ 1.5 times within 7 days, or a decrease in urine output < 0.5 mL/kg/h for 6 h [7]. In this article we present a case of a patient who was diagnosed with allopurinol-induced DRESS syndrome manifesting with typical skin changes accompanied by acute kidney injury.

CASE REPORT

A 46-year-old female patient with no previous nephrological history presented to the Emergency Department with weakness and accompanying skin rash. On admission, the patient complained of persistent itching and burning of the skin and numerous skin changes of the type of erythematous-pustular rash with scaling (Fig. 1, 2). These symptoms appeared about 72 hours before admission to the hospital. Initially, the skin changes involved only the face, then the whole body; at the same time, there was general weakness. The patient was initially treated in the Night and Holiday Medical Assistance Unit, where she received single doses of dexamethasone and clemastine — without effect. In her history, the patient reported (having had a) thrombosis of the superior mesenteric, splenic and portal veins 6 months earlier, complicated by acute mesenteric ischemia with subsequent resection of the ileum and creation of ileostomy; without changes in the arterial vessels (aorta, renal arteries). Due to the unclear etiology of thrombosis, the patient remained in the course of vascular and hematological diagnostics. In her history, she also reported a weight loss of 27 kg since the resection of the intestine. History for previous kidney diseases, hypertension, diabetes — negative. No abnormalities in the character and amount of urine output were found. The patient regularly received only rivaroxaban (20 mg/day) and folic acid (15 mg/day). Two weeks before admission to the Nephrology Department, due to hyperuricemia detected in a single measurement (serum uric acid level 16 mg/dL; without symptoms of gout) in primary health care conditions, allopurinol treatment (300 mg/day) was started.

The tests performed in the Emergency Department showed a significantly impaired renal excretory function with serum concentrations of creatinine 12 mg/dL (N: 0.5–1.1 mg/dL), urea 323 mg/dl N: 15–40 mg/dL)

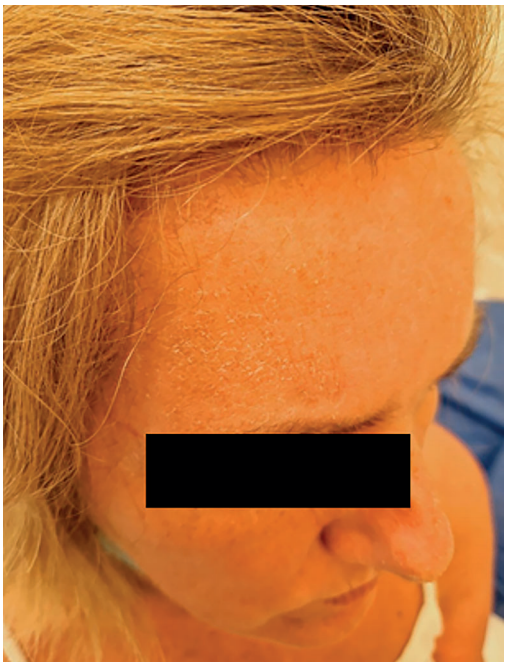


Figure 1. Skin lesions on admission — scaling

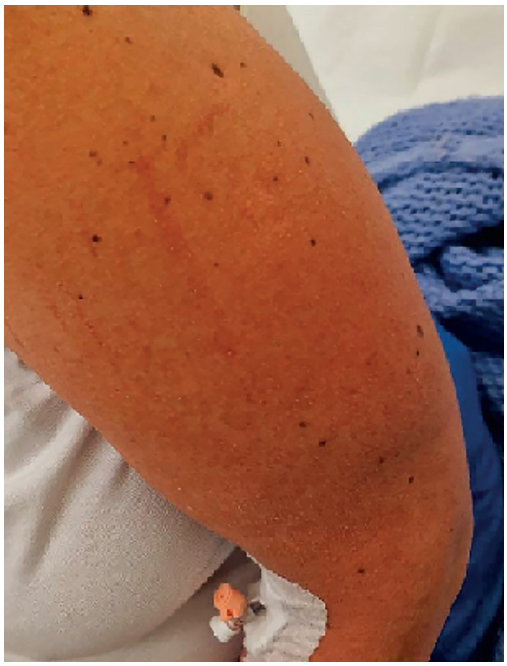


Figure 2. Skin lesions on admission — erythematous-pustular rash; excoriations

with coexisting compensated non-respiratory acidosis (pH 7.44 with pCO_2 24.5 mmHg and HCO3- concentration 16.5 mmol/L), without hyperkalemia. In addition, in the peripheral blood morphology, mild anemia (Hgb 11.9; N: 12–16 g/dL), leukocytosis 17.1 thousand/μL with eosinophilia 890/μL (5.2%) and normal platelet count 309 thousand/μL were observed. Notable were also increased concentration of inflammatory markers (CRP 87.8 mg/L; N: 0–5 mg/L) and markers of cardiac muscle damage (cTNI 17 ng/L; N: < 14 ng/L), increased activity of liver enzymes (AST 48 U/L, N: < 40 U/L; ALT 54 U/L, N: < 32 U/L; with normal level of total bilirubin 0.89 mg/dL, N: 0.2–1.1 mg/dL) and coagulation disturbances (APTT 45.1 s, N: 26–40 s; PT 34.5 s, N: 12–16 s).

Hyponatremia was also observed: Na+ — 115 mmol/l, and hypoproteinemia: TP — 55.3 g/L (possible complication after resection of the small intestine). Serum uric acid level was 2.8 mg/dl (N: 4–5 mg/dL). The urine test revealed proteinuria 0.56 g/L with active sediment (15 fresh red blood cells, without leached cells; N: 0–2; 15 white blood cells, N: 0–4; numerous bacteria in the field of view). The results of laboratory tests at admission, during hospitalization and after its completion are presented in Table 2.

In computed tomography, kidneys of 100 and 115 mm in size without signs of congestion, with increased echogenicity and signs of weaker contrast enhancement in the arterial and venous phase were visualized. Renal parenchymal layers of 18 mm thickness; in the upper pole of the right kidney, a 14 mm cyst with high-protein content (suspicion of blood content) was found, and in the calyx of the left kidney a 6 mm calculus. In Doppler ultrasound examination, high-resistance arterial flows were found in the cortical-medullary area of the kidneys — RI (Resistive Index): 0.78–0.82 (N: < 0.7). In imaging studies of the lungs, no significant deviations from the norm were found, no focal changes. Due to the history, characteristic skin changes, peripheral blood eosinophilia, signs of acute kidney, liver and cardiac muscle damage, a tentative diagnosis of DRESS in reaction to allopurinol was made. On the first day of hospitalization, allopurinol administration was discontinued, pulses of methylprednisolone were initiated (total dose of 1125 mg over 5 days), followed by conversion to oral prednisone (60 mg/d). Due to the symptoms of uremia, a temporary vascular access for hemodialysis was implanted and renal replacement therapy was started; 3 hemodialysis sessions were performed within 4 days.

Based on the clinical picture and additional tests performed (HIV Combo antigen test, HBs antigen concentration, anti-HBc and anti-HCV antibody titers, serum protein electrophoretic separation, ANA and ANCA titers, C3 and C4 complement components concentrations), other than DRESS possible

Table 2. Laboratory tests at admission, during hospitalization, and in the 2-month follow-up period

Parameter unit (reference value)	At admission	During hospitalization	Before discharge	2 months later
Hemoglobin g/dL (N: ♀ 12–16)	11.9 ↓	9.5 ↓	9 ↓	10.9 ↓
Leukocytes thousand/μL (N: 4–6)	17.1 ↑	7	8.9	13.4 ↑
Eosinophils cells/μL (N: 50–500)	890 ↑	600 ↑	400	–
Platelets thousand/μL (N: 150–400)	309	128 ↓	81 ↓	163
Creatinine mg/dL (N: ♀ 0.5–1.1)	12 ↑	2.94 ↑	1.45 ↑	1.08
Urea mg/dL (N: 15–40)	323 ↑	174 ↑	94 ↑	48 ↑
Uric acid mg/dL (N: ♀ 4–5)	2.8	7.7 ↑	6.5 ↑	4.4
Na^+ mmol/L (N: 145–145)	115 ↓	137	135	–
K^+ mmol/L (N: 3.5–5.1)	4.9	4.1	3.6	3.8
AST U/L (N: 5–40)	48 ↑	21	23	–
ALT U/L (N: 35–40)	54 ↑	39	45 ↑	–
cTNI ng/L (N: < 14)	17 ↑ → 13.4	–	–	–
CRP mg/dL (N: < 5)	87.8 ↑	2	5.7	–
Total protein (serum) g/L (N: 60–80)	55.3 ↓	–	–	–
Albumins g/L (N: 35–55)	38.3	32.1 ↓	–	–
Total protein (urine) ng/L (N: none)	0.56 ↑	–	0.49 ↑	–
APTT s (N: 25–40)	45.1 ↑	25.4	24.6	–
PT s (N: 12–16)	34.5 ↑	19.9 ↑	15.6	–
D-dimer ng/mL (N: 500)	890 ↑	< 270	–	–

causes of AKI were excluded, including viral infections, lymphatic system malignancies, acute cutaneous lupus erythematosus and vasculitis. Due to the lack of mucosal involvement, Stevens-Johnson syndrome was excluded. A biopsy of the pathologically altered skin was taken — the histopathological picture showed foci of chronic inflammation with numerous eosinophils; the result was obtained on the 3rd day of hospitalization. In the following days, a gradual improvement of the clinical condition was observed, with a reduction of skin changes with transient patchy peeling of the epidermis of the whole body. With the return of diuresis and observed improvement of renal excretory function, further procedures were discontinued. Due to the history of thrombosis and progressive decrease in platelet count (reduction to 81 thousand/μL, within 12 days of low molecular weight heparin administration), the diagnostics for hemostatic disorders were extended and increased activity of factor VIII and presence of antibodies against heparin-PF4 complex were found. In view of the above, anticoagulant therapy was modified again to rivaroxaban. Due to increasing anemia, 1 unit of irradiated leukocyte-poor red blood cell concentrate was transfused, obtaining stabilization of red blood cell parameters. Due to significant weight loss, signs of malnutrition (hypoproteinemia) and coexisting electrolyte disturbances, oral nutritional treatment was administered. After 21 days of hospitalization, the patient was discharged home in good general condition. On the day of discharge, slightly impaired renal excretory function persisted (serum creatinine concentration 1.16 mg/dL; eGFR according to CKD EPI formula 43 mL/min/1.73 m^2). Continuation of oral prednisone treatment at a dose of 1 mg/kg/day with gradual dose reduction by 5 mg every 2 weeks was recommended. In addition, rivaroxaban treatment (15 mg/d) was continued. Pantoprazole 40 mg/d was added. For the significant weight loss, oral treatment with a high-energy nutritional preparation was recommended.

DISCUSSION

DRESS syndrome is a rare acute drug reaction characterized by extensive rash with concomitant involvement of internal organs, lymphadenopathy and peripheral blood eosinophilia. Symptoms develop with a delay relative to the causative agent, typically from 2 to 6 weeks after exposure [4]. The risk of DRESS syndrome increases proportionally to the dose of the drug (causative agent). There is also an increased risk in patients with impaired renal

function and consequently impaired excretion of drugs; this applies especially to people treated with allopurinol, phenytoin and minocycline [8–10]. In the presented patient, the occurrence of DRESS syndrome may have been related to the administration of too high an initial dose of allopurinol (300 mg). The starting dose of allopurinol should be 100 mg/day or less, especially in patients with kidney failure. Gradual dose escalation is the key to minimizing the risk of adverse effects, such as DRESS syndrome. Predisposition to the development of DRESS for individual HLA polymorphisms and dependence on the polymorphism of genes encoding metabolizing enzymes (cytochrome P, N-acetyltransferase) have also been demonstrated [8–13]. Another interesting phenomenon described in the course of DRESS syndrome is reactivation of viruses from the Herpes viridae family (Epstein-Barr, cytomegalovirus, HHV-6, HHV-7); it occurs in up to 75% of patients, and its role in the pathogenesis of DRESS is unclear [14–18]. The first symptoms of DRESS are most often fever (75–90%), malaise and lymphadenopathy (54–65%). The characteristic skin reaction appears with a delay of 2 to 6 weeks; it occurs in 97% of cases and facilitates diagnosis. In almost 80% of cases, skin changes involve more than half of the body surface. The lesions are most often maculopapular (60%), less frequently generalized erythema (54%) may occur. A typical symptom is also facial edema (70%). In half of the cases, mucosal involvement of a mild course was observed. The occurrence of blisters, pustules and peeling of the epidermis was also described [5, 19]. In the presented patient, numerous erythematous-pustular changes were found — initially on the facial skin — then on the whole body, merging into generalized erythema. After a few days, patchy peeling of the epidermis occurred in the area of changes. The most common abnormalities in the laboratory tests are eosinophilia (82–95%), leukocytosis (95%), neutrophilia (78%), lymphocytosis (25–52%), monocytosis (69%) and presence of atypical lymphocytes (35–67%). In the described case, leukocytosis 17.1 thousand/μL, with neutrophilia 15.1 thousand/μl and eosinophilia 890/μL were observed. Involvement of at least one internal organ occurs in 90% of cases. About 35% of patients may have involvement of 2 organs, and involvement of at least 3 occurs in 20% of cases. Liver damage is the most common visceral manifestation of DRESS syndrome, occurring in 53–90% of cases. Pulmonary involvement symptoms occur in 30% of patients. Cardiac involvement occurring in 2–20% is associated with poor prognosis. Involvement of the central and peripheral nervous system is described in 2–8% of patients. In the discussed clinical situation, the patient suffered the involvement of two organs: skin and kidneys.

Relapses occur in 25% of patients, usually a few weeks/months after the symptoms have subsided. They are especially common in cases with rapid reduction of corticosteroid dose, therefore a gradual dose reduction is recommended for the patient. They may be induced by drugs other than the drug initially causing the symptoms. In patients who have had DRESS, an increased risk of developing autoimmune diseases, including autoimmune thyroiditis, vitiligo, systemic lupus erythematosus and type 1 diabetes, has also been reported, so patients should be closely monitored for the occurrence of these diseases in subsequent years [20–23]. Due to the great heterogeneity of clinical symptoms of DRESS, the decision on the intensity of treatment is based on the assessment of skin and internal organ involvement. Patients without clinical, laboratory or imaging evidence of organ involvement may be treated symptomatically with topical corticosteroids. Additionally, to alleviate symptoms, antihistamines and emollients may be considered in treatment. In case of the presence of organ changes, oral preparations of prednisone are used, until clinical improvement and normalization of laboratory parameters are achieved, at an initial dose of 0.5 to 1 mg/kg per day, gradually reduced over 8–12 weeks. In severe cases, intravenous methylprednisolone (250 to 500 mg per day for two to four days) is recommended, followed by conversion to oral steroid [24]. Most patients with DRESS syndrome return to full health within a few weeks to a few months after discontinuation of the drug. Also in the described case, renal function recovery was observed (serum creatinine concentration after 2 months — 1.08 mg/dL, eGFR 64 mL/min/1.73 m^2), and serum uric acid concentration remained in the range of 4–5 mg/dL. In the described case, hypouricemic treatment was not continued; in patients requiring further treatment, due to exclusion of allopurinol from further use other drugs lowering the uric acid level can be considered, e.g. febuxostat (liver metabolism), especially in patients with impaired renal function [25]. According to the ACR 2020 guidelines (American College of

Rheumatology), treatment can be extended with uricosuric drugs - probenecid, benzbromarone, sulfinpyrazone, which however require preserved renal excretory function and which, unfortunately, are not available in Poland. In the next step, in case of their ineffectiveness, pegloticase can be included. Flozins and some sartans (losartan, irbesartan) [26] used for nephroprotection in patients with chronic kidney disease with albuminuria also have hypouricemic potential. Drugs that should be avoided, i.e. those increasing uric acid level, are acetylsalicylic acid and loop and thiazide diuretics.

According to a recent systematic review regarding DRESS syndrome with kidney manifestations, most of 71 cases identified in the literature were associated with antibiotics (34%) — most commonly vancomycin (24%) — xanthine oxidase inhibitors (15%) and anticonvulsants (11%). The kidneys were the only visceral organ affected in 21% of cases, while both liver and kidneys were involved in 54% of patients. AKI was the predominant kidney manifestation, occurring in 96% of cases, with anuria in 4% of cases, and need for temporary renal replacement therapy in 30% of cases. Isolated proteinuria or hematuria were found only in 4% of patients. However, almost all patients recovered full kidney function, confirming an overall favorable prognosis despite the initial severity of the disease. Mortality in described cohort was 13%, which is higher than previously reported, and was negatively associated with female sex (22.6% *vs.* 5%). Factors such as class of medication taken, latency period or pre-existing kidney disease did not correlate with higher mortality rates [27].

CONCLUSIONS

DRESS syndrome is a rare but potentially fatal hypersensitivity reaction that requires rapid diagnosis and early treatment. In the diagnosis, a detailed medical history is essential, in which the first thing to pay attention to is the dynamics of the symptoms and their temporal correlation with the introduction of a new, syndrome inducing drug. Characteristic skin changes with accompanying peripheral blood eosinophilia are particularly helpful in making the diagnosis. In the described case, typical symptoms: fever, extensive skin changes with eosinophilia, increased liver enzyme activity, biochemical signs of kidney damage and the correlation between symptoms and initiation of allopurinol treatment allowed for a quick diagnosis (5 points on the RegiSCAR scale), initiation of proper treatment and achievement of complete remission.

Conflict of interest

The authors declare no conflict of interest.

References

1. Wolfson AR, Zhou Li, Li Yu, et al. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome Identified in the Electronic Health Record Allergy Module. J Allergy Clin Immunol Pract. 2019; 7(2): 633–640, doi: 10.1016/j.jaip.2018.08.013, indexed in Pubmed: 30176295.
2. Abdelnabi M, Elmssary M, Sekhon J, et al. Acute onset of fever, eosinophilia, rash, acute kidney injury, and a positive Monospot test in a patient on lamotrigine: DRESS syndrome. Lancet. 2022; 399(10338): 1902, doi: 10.1016/S0140-6736(22)00464-0, indexed in Pubmed: 35569467.
3. Knowles SR, Shapiro LE, Shear NH. Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. Drug Saf. 1999; 21(6): 489–501, doi: 10.2165/00002018-199921060-00005, indexed in Pubmed: 10612272.
4. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: Part I. Clinical perspectives. J Am Acad Dermatol. 2013; 68(5): 693.e1–14; quiz 706, doi: 10.1016/j.jaad.2013.01.033, indexed in Pubmed: 23602182.
5. Kardaun SH, Sekula P, Valeyrie-Allanore L, et al. RegiSCAR study group. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol. 2013; 169(5): 1071–1080, doi: 10.1111/bjd.12501, indexed in Pubmed: 23855313.
6. Kano Y, Shiohara T. The variable clinical picture of drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms in relation to the eliciting drug. Immunol Allergy Clin North Am. 2009; 29(3): 481–501, doi: 10.1016/j.iac.2009.04.007, indexed in Pubmed: 19563993.
7. Summary of Recommendation Statements. Kidney Int Suppl (2011). 2012; 2(1): 8–12, doi: 10.1038/kisup.2012.7, indexed in Pubmed: 25018916.
8. Maubec E, Wolkenstein P, Loriot MA, et al. Minocycline-induced DRESS: evidence for accumulation of the culprit drug. Dermatology. 2008; 216(3): 200–204, doi: 10.1159/000112926, indexed in Pubmed: 18182810.
9. Chung WH, Chang WC, Lee YS, et al. Taiwan Severe Cutaneous Adverse Reaction Consortium, Japan Pharmacogenomics Data Science Consortium. Genetic variants associated with phenytoin-related severe cutaneous adverse reactions. JAMA. 2014; 312(5): 525–534, doi: 10.1001/jama.2014.7859, indexed in Pubmed: 25096692.
10. Ng CY, Yeh YT, Wang CW, et al. Taiwan Severe Cutaneous Adverse Reaction Consortium. Impact of the HLA-B(*)58:01 Allele and Renal Impairment on Allopurinol-Induced Cutaneous Adverse Reactions. J Invest Dermatol. 2016; 136(7): 1373–1381, doi: 10.1016/j.jid.2016.02.808, indexed in Pubmed: 26996548.
11. Konvinse KC, Trubiano JA, Pavlos R, et al. HLA-A*32:01 is strongly associated with vancomycin-induced drug reaction with eosinophilia and systemic symptoms. J Allergy

Clin Immunol. 2019; 144(1): 183–192, doi: 10.1016/j.jaci.2019.01.045, indexed in Pubmed: 30776417.
12. Cho YT, Yang CW, Chu CY. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): An Interplay among Drugs, Viruses, and Immune System. Int J Mol Sci. 2017; 18(6), doi: 10.3390/ijms18061243, indexed in Pubmed: 28598363.
13. Phillips E, Chung WH, Mockenhaupt M, et al. Drug hypersensitivity: Pharmacogenetics and clinical syndromes. Journal of Allergy and Clinical Immunology. 2011; 127(3): S60–S66, doi: 10.1016/j.jaci.2010.11.046.
14. Sekiguchi A, Kashiwagi T, Ishida-Yamamoto A, et al. Drug-induced hypersensitivity syndrome due to mexiletine associated with human herpes virus 6 and cytomegalovirus reactivation. J Dermatol. 2005; 32(4): 278–281, doi: 10.1111/j.1346-8138.2005.tb00762.x, indexed in Pubmed: 15863850.
15. Descamps V, Brunet-Possenti F. Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. Arch Dermatol. 2001; 137(3): 301–304.
16. Kano Y, Hiraharas K, Sakuma K, et al. Several herpesviruses can reactivate in a severe drug-induced multiorgan reaction in the same sequential order as in graft-versus-host disease. Br J Dermatol. 2006; 155(2): 301–306, doi: 10.1111/j.1365-2133.2006.07238.x, indexed in Pubmed: 16882166.
17. Tohyama M, Hashimoto K, Yasukawa M, et al. Association of human herpesvirus 6 reactivation with the flaring and severity of drug-induced hypersensitivity syndrome. Br J Dermatol. 2007; 157(5): 934–940, doi: 10.1111/j.1365-2133.2007.08167.x, indexed in Pubmed: 17854362.
18. Picard D, Janela B, Descamps V, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): a multiorgan antiviral T cell response. Sci Transl Med. 2010; 2(46): 46ra62, doi: 10.1126/scitranslmed.3001116, indexed in Pubmed: 20739682.
19. Chen YC, Chiu HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. Arch Dermatol. 2010; 146(12): 1373–1379, doi: 10.1001/archdermatol.2010.198, indexed in Pubmed: 20713773.
20. Onuma H, Tohyama M, Imagawa A, et al. Japan Diabetes Society Committee on Type 1 Diabetes Mellitus Research, Japanese Dermatological Association. High frequency of HLA B62 in fulminant type 1 diabetes with the drug-induced hypersensitivity syndrome. J Clin Endocrinol Metab. 2012; 97(12): E2277–E2281, doi: 10.1210/jc.2012-2054, indexed in Pubmed: 23071161.
21. Lian B, Busmanis I, Lee H. Relapsing Course of Sulfasalazine-Induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Complicated by Alopecia Universalis and Vitiligo. Annals of the Academy of Medicine, Singapore. 2018; 47(11): 492–493, doi: 10.47102/annals-acadmedsg.v47n11p492.
22. Ushigome Y, Kano Y, Ishida T, et al. Short- and long-term outcomes of 34 patients with drug-induced hypersensitivity syndrome in a single institution. J Am Acad Dermatol. 2013; 68(5): 721–728, doi: 10.1016/j.jaad.2012.10.017, indexed in Pubmed: 23182063.
23. Chen YC, Chang CY, Cho YT, et al. Long-term sequelae of drug reaction with eosinophilia and systemic symptoms: a retrospective cohort study from Taiwan. J Am Acad Dermatol. 2013; 68(3): 459–465, doi: 10.1016/j.jaad.2012.08.009, indexed in Pubmed: 22959230.
24. Roujeau JC, Haddad C, Paulmann M, et al. Management of nonimmediate hypersensitivity reactions to drugs. Immunol Allergy Clin North Am. 2014; 34(3): 473–87, vii, doi: 10.1016/j.iac.2014.04.012, indexed in Pubmed: 25017673.
25. Lin TC, Hung LY, Chen YC, et al. Effects of febuxostat on renal function in patients with chronic kidney disease: A systematic review and meta-analysis. Medicine (Baltimore). 2019; 98(29): e16311, doi: 10.1097/MD.0000000000016311, indexed in Pubmed: 31335677.
26. Chida R, Hisauchi I, Toyoda S, et al. Impact of irbesartan, an angiotensin receptor blocker, on uric acid level and oxidative stress in high-risk hypertension patients. Hypertens Res. 2015; 38(11): 765–769, doi: 10.1038/hr.2015.82, indexed in Pubmed: 26178150.
27. Dagnon da Silva M, Domingues SM, Oluic S, et al. Renal Manifestations of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome: A Systematic Review of 71 Cases. J Clin Med. 2023; 12(14), doi: 10.3390/jcm12144576, indexed in Pubmed: 37510691.

Renal Disease and Transplantation Forum
2023, vol. 16, no. 3, 142–146

ISSN 2720–2771
e-ISSN: 2720-4189
DOI: 10.5603/rdtf.98600

John Feehally[1], Janusz Ostrowski [2, 3]

[1]Emeritus Consultant Nephrologist, Leicester, UK; Honorary Professor of Renal Medicine, University of Leicester, UK
[2]Deparment of the History of Medicine, School of Public Health, Centre of Postgraduate Medical Education, Warsaw, Poland
[3]Historical Section of the Polish Society of Nephrology

Professor Stewart Cameron (1934–2023) — The Legend. In Memoriam

Abstract

It was in the second half of the 20th century when the first clinics and societies of nephrology started to spring across Europe, triggering the intensive development of the new medical specialty which had just emerged from internal medicine. The process had its outstanding leaders, among whom was Professor Stewart Cameron, who died in July 2023. This paper is a short attempt to summarise S. Cameron's achievements.

Key words: history of nephrology, giants in nephrology, Stewart Cameron

INTRODUCTION

After World War II, a new field of medicine, known as nephrology, started to emerge from the more general internal medicine. At the forefront of the process were many outstanding figures, among whom was the world-famous British professor — Stewart Cameron.

Stewart Cameron established modern nephrology at Guy's Hospital. London following in the footsteps of one of his heroes, Richard Bright, the 19th century Guy's physician who was one of the first influential figures in the study of kidney disease. Cameron's impact on Guy's was formidable, but so much more was his influence on nephrology throughout the UK and across the world. He was one of the world's leading nephrologists in the second half of the 20th century. His supreme gifts of intelligence, articulacy and leadership were matched by his innate modesty and his unending concern for the careers of others.

John Stewart Cameron (but always known as Stewart) was born on 5th July 1934 in Aberdeen, Great Britain, where his father was in the merchant navy, but the family moved to London in 1946 where his father worked in film production at Ealing Studios. Stewart was a gifted draughtsman (as had been his father) and for a time considered going to art school but instead decided to pursue a career in medicine. At first he planned to return to Aberdeen University to study, however differences in school qualifications between England and Scotland meant this was not straightforward, so instead he entered Guy's in 1953 (Fig. 1).

He got 1st Class Honours in an intercalated BSc in physiology, and from then on was determined to be a clinician scientist. He graduated MB BS with Distinction in 1959. Unsure at first the branch of medicine he would pursue, Professor John Butterfield at Guy's became his mentor, and he began to study diabetes. But nephrology had grabbed his interest, not least when he read The Kidney: Structure and Function in Health and Disease (1951) by Homer Smith which was the brilliant definitive book on renal physiology at the time. Butterfield arranged for him to go to Cornell University, New York supported by a Fulbright Scholarship to work in nephrology with E Lovell 'Stretch' Becker and Robert F Pitts. Before he went, he and John Trounce, a clinical pharmacologist, had already established at Guy's the beginnings of a renal unit, including dialysis for acute renal failure [1].

After his time in New York he was determined to make nephrology his career. He returned in 1963 as Lecturer in the Department

Address for correspondence:
Ass. Professor Janusz Ostrowski, MD, PhD
Department of the History of Medicine
Centre of Postgraduate Medical Education
ul. Kleczewska 61/63
01-826 Warsaw, Poland
e-mail: janusz.ostrowski@cmkp.edu.pl

Figure 1. John Stewart Cameron (photo Janusz Ostrowski)

of Medicine at Guy's, and wrote his MD thesis on glomerular permeability to proteins in the nephrotic syndrome, based on his work at Cornell. From 1967 he was Senior Lecturer in Medicine at Guy's, then Professor of Renal Medicine in 1974, and from 1975 Director of the Clinical Sciences Laboratories at Guy's. He held both these positions until his retirement.

This was an exciting time to be a nephrologist. People with irreversible kidney failure (a uniformly fatal condition until then) were becoming treatable; the possibility loomed of giving them even years of extra life through dialysis treatment or a kidney transplant. While in New York Cameron had seen something of these emerging techniques, but they were only just beginning in the UK, and it was clear that they were complex and demanding — both for patients and doctors. The work required practicality and passion, and could only be delivered successfully by those willing to commit their emotional and intellectual energy unstintingly. Cameron had found his metier, and from the mid-1960s he set off to establish a renal unit at Guy's, which had been selected by the Department of Health as one of several pilot dialysis units being trialled in the UK. Recognising from the beginning that a chronic dialysis programme on its own carried the risk of unsustainable growth as more and more patients began treatment, he realised that the ideal strategy was to develop in parallel a kidney transplantation programme.

He was joined by Chisholm Ogg, at first his registrar, and soon his consultant colleague. Together they built a unit which set the standards, and became well known far and wide. Collaborative teamwork was the watchword. All were partners in the kidney family — patients and staff alike. Nurses, technicians, dietitians and many others knew they were respected members of the team and responded to the responsibility and autonomy they were being given. First names were the norm, far from the tradition of the time. Such team working was innovative and unique to nephrology at the time, now it is everywhere in medicine.

The work was all-consuming - their success meant patients requiring treatment for kidney failure came flooding in. They were even treating children as well as adults until Cyril Chantler joined them as a paediatric nephrologist in the early 1970s. Cameron described just how exciting it was in those early days, every day bringing a new challenge, a new opportunity - so much to learn, so much to do. They were giving it everything but there was a price. A hepatitis epidemic swept through the Guy's renal unit in 1969, and Cameron himself was for a time severely ill with hepatitis B.

Figure 2. John Stewart Cameron receiving an award for scientific achievements from the President of ERA-EDTA Prof. Raymond Vanholder during the ERA-EDTA Congress in Paris, France in 2012 (Photo Janusz Ostrowski)

But the Guy's unit flourished and grew, many more joined the staff, and soon the unit had an international reputation, receiving visitors from all over the world.

Developing the Guy's unit would be a career high for many, but Cameron was just beginning.

He was always determined that Guy's would be a place where research flourished alongside clinical work. He had an encyclopaedic knowledge of the whole of kidney disease, but it was in the study of glomerulonephritis, immune-mediated kidney disease, he especially made his mark. Following in the tradition of Richard Bright, Cameron recognised the importance of longitudinal study of personally observed cases as the means to understand how disease progresses. Alongside clinical observation Bright had used the best available material for laboratory study — in his case only autopsy kidneys (some of Bright's which studied are still in the Guy's Museum). Alongside clinical observation Cameron could use the insights now being provided by the study of kidney biopsies, as well as new serological tests, for example tests of lupus and for complement activation.

He became a world leader in the study of the natural history of glomerular disease. He made outstanding contributions in glomerulonephritis, nephrotic syndrome, and lupus nephritis, as well as renal transplantation in adults and children. He was also an authority on altered urate and purine metabolism and their impact on the kidney, working with Anne Simmonds. He wrote fluently, and in the end his published output was formidable: more than 450 research papers, over a hundred book chapters, and a dozen books large and small. He was a founding editor of the Oxford Textbook of Clinical Nephrology now in its 4th Edition [2].

And he lectured brilliantly. When Cameron went to the rostrum, he commanded your attention. He became a ubiquitous presence at national and international meetings on glomerulonephritis. If you saw his name was not on the programme, your heart sank a little because you knew that without him the meeting would generate less energy, less intellectual force, less joie de vivre.

Clinician and researcher, that would be a career high for most, but Cameron still had so much more to give. Ideally suited he was soon drawn into leadership in the kidney world beyond Guy's — becoming President not only of the Renal Association in the UK, but also of EDTA-ERA and the International Society of Nephrology. In the early 1990s he even allowed himself to be president of both the Renal Association and the ISN at the same time — an impossible workload for anyone less gi-

Figure 3. Stewart Cameron with his wife, Alison, during the IAHN Congress in Wieniec-Zdroj, Poland in 2017 (Photo Grzegorz Główczyński)

fted or committed [3]. Back in 2012, during the ERA-EDTA Congress in Paris, France, he received an award for outstanding achievements in the field of science (Fig. 2). S. Cameron also played a very active part in the International Association for the History of Nephrology (IAHN), whose honorary member he became in 2013 during the congress in Patras-Olympia, Greece.

His international leadership was not just titular, he did not sit at home directing traffic, he travelled the world teaching in many different settings, and especially encouraging the emergence of nephrology in low resource countries. With his gift for friendship and his unrelenting energy, he was a much-loved mentor to hundreds of nephrologists, many of whom came from abroad to Guy's and then returned to their own countries.

But it is more than the sum of all this work for which he should be remembered. Rather It is for the way he bore all his gifts. His complete lack of self-importance, despite his remarkable talents, his enthusiasm for the work of others, his encouragement of those many he mentored whose names and personal circumstance he never forgot – it is these for which he is most loved.

Cyril Chantler described him best: 'Stewart was the most curiously intelligent doctor I have ever known. We used to say at Guy's if you wanted to know something about anything you had to go the library……. or better still….. ask Stewart.' Any conversation with him was a delight, a chance to learn. He was an extraordinary multilingual polymath, he read widely and voraciously. It seemed he knew more than anyone about everything - especially nephrology, and the history of nephrology. But equally about the poet John Keats (who had been a Guy's medical student), and rock climbing, and Gaelic poetry, and history, and wildlife, and so much more. Yet he was never grand about it, he simply loved knowledge, and loved sharing it.

Unusually for those days he had married and had two children while still a medical student, a choice somewhat frowned upon at the time by the Guy's establishment, some of whom wrongly suggested to him it might hamper his career development. Margot was a perfect foil and partner for him, and she joined him regularly on his nephrology travels.

When still at the height of his powers, he was forced to retire early from clinical and academic work following complications after urgent cardiac surgery. He retired to the beautiful hill country of Cumbria in north west England, and though dogged subsequently by ill health he continued to write energetically across the range of his interests (including for example an extensive history of the Ross of Mull) and

immersing himself in village life. When Margot developed dementia, he cared for her devotedly at home until her death. Emerging from his bereavement, he in due course found great happiness with Alison (née Russell) whom he met again forty three years after she had been a ward sister at Guy's. Together they had written in 1971 the first book on nursing aspects of renal disease, dialysis and transplantation; they married in 2018 (Fig. 3) [4].

CONCLUSION

John Stewart Cameron passed away on 30th July 2023 at the age of 89. He had bestridden the world of nephrology. Once in a generation comes such a doctor whose natural gifts, intellect, energy, and modesty put them head and shoulders above us all. Greatness borne so lightly is a wonderful thing.

References

1. Ogg C. Stewart Cameron. Nephrology Dialysis Transplantation. 1997; 12(6): 1298–1298, doi: 10.1093/ndt/12.6.1298.
2. Losito A, Fogazzi G. In ricordo John Stewart Cameron. Giornale Italiano di Nefrologia. ; 2023: 4.
3. Rees A. Presentation of the 2003 Jen Hamburger Award to J. Stewart Cameron. Kidney Int. 2003; 64: 1933–1944.
4. Glassock RJ, Feehally J. In memoriam: Stewart Cameron (1934-2023). Kidney Int. 2023 [Epub ahead of print], doi: 10.1016/j.kint.2023.08.018, indexed in Pubmed: 37716707.