REVIEW ARTICLE

Immunosuppressive therapy in glomerular diseases

Major accomplishment of Tadeusz Orłowski and his school

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ABSTRACT

Glomerulopathies are the third most common cause of end-stage renal failure. Immunosuppressive treatment of glomerulonephritis in a systematic way was introduced in Poland by Professor Tadeusz Orłowski in the early 1960s. The studies were conducted at the First Department of Medicine and at the Transplantation Institute of the Medical Academy in Warsaw in the years 1962–1988. This paper critically reviews the results of studies on the use of combined, triple-drug (prednisone/chlorambucil/azathioprine), immunosuppressive protocol in various pathological forms of glomerulopathies. We conclude that immunosuppressive protocols pioneered by Tadeusz Orłowski continue to be the backbone of the treatment of glomerulonephritis, especially the one with nephrotic syndrome, progressive impairment of kidney function and poor prognosis.

In a humble assessment of his own professional achievements, professor Tadeusz Orłowski paid great attention to the studies that aimed to elucidate the role of immunosuppressive therapies in glomerulopathies. In fact, to those who were his close co-workers in the First Department of Medicine and then Transplantation Institute and to those who participated in the studies, it was essential as well.

Glomerulonephritis (GN) continues to be the third most common cause of end-stage renal failure. Recent US Renal Data System indicates that patients with GN constitute 8.2% of incident and 15.6% of prevalent dialysis patients in the United States.[1] This percentage very likely underestimates the incidence of GN, mainly due to two factors: an overestimation of hypertensive disease as a cause of end-stage renal disease in patients with late clinical presentation and scarce symptomatology and a low rate of kidney biopsies. In children and young adults, GN is more prevalent in the dialysis population than in the elderly and carries significant burden to the overall health and well-being of the society. Although progress has been made in the understanding of the biology/function and the genetics of glomerular cells, as well as the response of glomerular structure to the immune/inflammatory injury, the therapeutic interventions are far from being uniformly successful and accepted. This was even more evident in the early 1950s when a young physician, Tadeusz Orłowski, started his career.

At that time (1955–1965), GN was the most common renal disease in Poland and Europe, leading to renal failure and to death, since neither dialysis nor transplantation was widely available. Thus, the work toward better understanding and treating GN was indeed the priority.

The early 1950s were also a time of confusion in the descriptive pathology of GN, especially when Arthur Ellis introduced a simplified classification, based on long-term studies of 400 patients with nephritic syndrome. Ellis divided GN into type I, those with inflammatory nephritis (mainly, as he thought, due to streptococcal or other infection), and type II, degenerative disease (membranous and lipoid nephrosis).[2] Clinical

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observation on "acute", "subacute" or "chronic" GN had no translation into what a pathologist understood by those terms. A major change occurred with the introduction of a modern renal biopsy technique by Muehrcke and Kark in 1954.[3] The use of a Vim-Silverman needle in modification of the Franklin, Muerhcke and Kark's technique allowed physicians to perform a biopsy in the early course of nephrotic syndrome and to repeat it in clinically justifiable cases. This led to the realization that the various pathological forms of GN were not a *continuum* but rather part of distinct clinico-pathological entities. By 1961, approximately 5,000 biopsies were done worldwide, 1,450 in Chicago, 840 in Copenhagen and the rest in 12 other centers.[4]

In the same year (1961), the first three kidney biopsies were performed by Tadeusz Orłowski in patients from the First Department of Medicine of Warsaw Medical Academy. Subsequently, biopsies were done routinely by Mieczysław Lao, Liliana Gradowska and members of the young generation of physicians. Initially, these biopsies were performed using the "blind technique", later utilizing intravenous contrast and television fluoroscopic monitoring, and finally under ultrasound guidance. Soon it became clear that a pathologist committed to kidney diseases had to be part of the Glomerulonephritis and Transplant Team. Thus, since 1970 Jagna Glyda and later Maria Morzycka have come to be dedicated pathologists responsible for kidney pathology assessments. Thin cutting slides, a prerequisite for proper light microscopy staining (hematoxylin and eosin [H&E], periodic acid-Schiff [PAS], Masson and Jones) were used with further addition of immunofluorescence and electron microscopy (the latter was not used in each case). The incorporation of a renal pathology laboratory into the Department of Medicine/Transplantation Institute greatly improved the communication within the Glomerulonephritis Team and allowed all members to be proficient in biopsy reading. Furthermore, it had a great impact on the immediate delivery of care, particularly for post-transplant patients with acute rejection. Needless to say, Tadeusz Orłowski paid great attention to biopsy interpretation himself and spent time acquiring necessary knowledge in the laboratory of a renowned French nephropathologist, Renee Habib, in Necker Hospital in Paris. The Visiting Professors Program, sponsored by the Polish Academy of Sciences, also facilitated international exchange of knowledge with widely recognized experts in the field.

The development of the combined (prednisone with azathioprine and chlorambucil) immunosuppressive protocol for the treatment of glomerulopathies with and without nephrotic syndrome was a long and complicated process. The first patients were treated in an organized way in 1962, but the studies published in 1968 had analyzed clinical response to the combined therapy since 1964.[5] The rationale behind this observational prospective study was the finding that steroid therapy alone was not effective in the treatment of adult nephrotic syndrome, which prompted Tadeusz Orłowski to use combined immunosuppressive therapy. There were 29 patients (19 males and 10 females); 24 patients had kidney biopsy evaluated only by light microscopy (H&E and PAS staining only).

The pathology was still described according to the Ellis criteria. Using the current criteria, this would correspond to 12 patients possibly having membrano-proliferative GN with hypocomplementemia and proliferative changes and a course of the disease lasting >3 months; 5 patients having membranous GN; 4 patients with rapidly progressive GN; 3 patients with amyloidosis, 1 patient with systemic lupus erythomatosus, and 1 with a minimal change. It should be noted, that immunoglobulin A (IgA) nephropathy had not been recognized until Berger's publication in 1968.[6] Fourteen patients did not respond to previous steroid therapy, 15 subjects had not been previously treated. The combined protocol initially included prednisone in a dose of 1 mg/kg body weight, 6-mercaptopurine or azathioprine in a daily dose of 50–150 mg and chlorambucil in a daily dose of 2 mg. Medications were continued for 3–40 weeks depending on the patient's outcome and response. All patients had nephrotic syndrome (proteinuria 3.0–27.5 g/24 h; 9.0 ±5.1), 10 patients had creatinine clearance <25ml/min (14.3 ±6.9) on enrollment into the study, while 19 patients had creatinine clearance >40 ml/min (82.5 ±25.2). Response to the therapy was graded as very good (proteinuria <1.0 g/day, normal protein/creatinine ratio [Pcr]), good (reduction in proteinuria <3g/day with normal or improved Pcr), poor (reduction in proteinuria <3g/day without improvement in kidney function or *vice versa*), and bad (no change or deterioration of proteinuria or Pcr).

A positive response (very good and good) was obtained in 12 patients, a bad outcome in 16 patients and poor in 1 patient. Proliferative GN's responded in 55% of patients and good response was more likely to occur in patients with preserved kidney function at the beginning of the therapy. In some cases the rapid withdrawal of immunosuppression led to recurrence of proteinuria, which responded to intensification of the therapy. The treatment failed in amyloidosis and in two cases of membranous GN. Study data published in contemporary literature (155 patients studied) showed 10% full and 30% partial remission response to steroid therapy in proliferative GN. The authors were aware that there was no control group in the study, which was also a common finding in the literature of that period. Control groups were not used for ethical reasons; treatment was seen *a priori* as giving the best chance for kidney function preservation, as long as no harm was caused by the treatment. A small number of side effects were observed, resulting mainly from high doses of steroids used in the first weeks

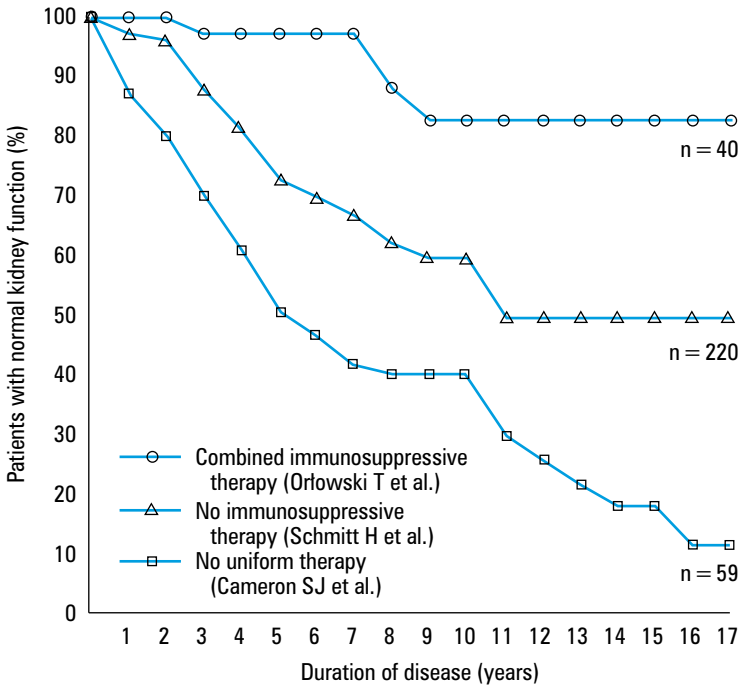

FIGURE The results of the triple drug immunosuppressive therapy in primary membranoproliferative type I glomerulonephritis

of the therapy; leucopenia and thrombocytopenia were relatively frequent and required dose adjustment, but did not lead to discontinuation of the treatment. The overall results were seen as encouraging but requiring further studies.

The second published study[7] used the modern renal pathology classification (as we know it today), similar to the one used in the steroid study of the Medical Research Council in Great Britain,[8] but without recognition as yet of IgA nephropathy. Begun in 1962, this study followed a total of 106 patients for a period ranging from 6 months to 10 years (a mean of 2 years). The patients were treated with 8 different regimens. The combined regimen (n = 39) had 3 drugs: prednisone 5–60 mg/day, and 6-mercaptopurine 0.75 mg/kg/24 h or azathioprine 1–3mg/kg/24 h, and chlorambucil 2–6 mg/24 h or cyclophospamide 0.75–2 mg/24 h. Other regimens included both prednisone and one of the above immunosuppressive agents or prednisone with indomethacin (25–150 mg/24 h). The latter agent gained popularity following Michielsen's findings,[9] but was later abandoned due to a low success rate and side effects that included interstitial nephritis with nephritic syndrome. The authors concluded that "only the combined triple-drug therapy, when started in patients with good renal function have given complete or partial remission in most cases (83% of cases). Other methods were less effective... In cases of proliferative GN the frequency of total remission was much higher than in control series reported by Medical Research Council".[7]

Another important conclusion was that repeated control biopsies evidently proved that "the clinical remission, even complete, was usually not associated with definite improvement of renal histology".[7] The weakness of that study was the lack of statistical analysis and the heterogeneity of GN in each of the treated groups, but a detailed documentation provided in the paper will allow to reanalyze the data in the future.

A subsequent study, published in 1988, focused on single glomerulopathy, idiopathic membranoproliferative type I GN.[10] The diagnosis was based on light and immunofluorescence microscopy using standard criteria. Forty patients with nephritic range proteinuria were treated with combined immunosuppression of a full starting dose for 8.2 ±0.9 months followed by reduction in prednisone dose every other day, azathioprine dose up to 50 mg/24 h and chlorambucil dose up to 2 mg/24 h. Twelve patients stopped treatment after a mean of 57 ±13.6 months of therapy. The cumulative kidney survival was calculated for 5, 10 and 15 years and compared with the data from the study by Cameron et al.[11,12] The results are presented in the **FIGURE**[13].

There was a better kidney survival in the combined therapy compared to mostly untreated patients in the study by Cameron et al. and to the data presented by Schmitt et al. in which study subjects were treated with a non-uniform protocol.[11,12] It should be noted that different populations with a different level of general medical care were compared, which might have affected kidney survival. Moreover, only patients with nephritic syndrome were treated by the combined protocol and the duration of intensive immunosuppression had to be planned carefully. Orłowski et al. concluded that "the protocol should be performed until the first signs of improvement appeared, e.g. reduction in proteinuria and/or hematuria. Furthermore, careful instruction and monitoring of patients was of utmost importance, and all contraindications to such form of treatment had to be respected".[7]

Finally, the role of immunosuppressive drugs had been studied in a prospective way in 33 patients with IgA nephropathy in the years 1969–1988.[14] IgA nephropathy has a variable natural course characterized by periods of relative quiescence, mixed with relapses of proteinuria, finally leading to a gradual progression of end-stage renal diseases. During the study, patients were followed, and depending on their clinical presentation (only hematuria, hematuria with proteinuria, nephritic syndrome with deterioration of kidney function), they were assigned for a period of symptomatic treatment only (28 periods), triple immunosuppressive therapy (21 periods), immunomodulation with thymosin (10 periods) and dipyridamole plus aspirin (4 periods). By design, patients treated with immunosuppression presented with either nephritic syndrome or deteriorated kidney function. Cumulative kidney survival at 5, 10 and 15 years was 97%, 93%, and 93%, respectively. Thymosin and dipyridamole did not modify the course of IgA nephropathy. Significant decrease in proteinuria, remission of nephritic syndrome, and stabilization of kidney function were observed in patients treated with immunosuppression. No serious complications

during immunosuppressive therapy were observed. The number of bacterial and viral infections were comparable in all groups of patients.

Interestingly, in all 4 papers of Orłowski et al. little attention was paid to the general management of patients with GN. Great attention was given to the treatment of hypertension, but not to achieving the current standard of 125/75 mmHg. In addition, a low salt diet and a variable protein content diet (1–2 g/kg body weight plus urinary losses of protein) were advocated. Edema was treated with diuretics and infections were treated appropriately. Patients had been regularly monitored for early detection of any side effects associated with the therapy, particularly those related to steroids. The current, radical approach to reduce proteinuria using angiotensin-converting enzyme inhibitors (ACEI) and/or an angiotensin II receptor blocker (ARB) was not available at the time of the studies. Screening for renal vein thrombosis in membranous nephropathy, a standard procedure today, was not performed due to the lack of high resolution ultrasound.

Nearly 50 years have passed since the first studies on immunosuppressive therapy were started, but we still face many questions concerning the procedure. Is immunosuppressive therapy effective? Which agents are most useful? What is the optimal duration of therapy? How to treat relapses? What is the risk-benefit ratio acceptable for individual patient?

The data available in the current literature gives only partial answers to these questions. The armamentarium of potentially effective agents increased significantly. Calcineurin inhibitors, sirolimus and mycophenolate mofetil, have been introduced into transplantation, and later into the treatment of GN during the last 15 years. Biological agents, including intravenous immunoglobulin and anti-CD20 chimeric antibody (rituximab), have proved useful in some GN types. Finally, a wide group of blockers of co-stimulatory pathways on T cells and other modulators of immune response will be soon tested with relation to their effect on glomerulopathies.[15] These advances, however, do not offer definitive solutions.

Given the complexity of the issue, it is impossible to present up-to-date, comprehensive and accurate recommendations on the use of immunosuppressive agents in individual glomerulopathies in this paper. The approach to the treatment of IgA nephropathy, the most common GN, can serve as an example. The value of ACEI and ARB appears to be well established. The use of steroids in patients with IgA and proteinuria/nephrotic syndrome,[16] combined regimens of prednisolone, cyclophosphamide, and azathioprine,[17] and ω-3 fatty acids[18] have their advocates and can be applied effectively to a specific target population. However, in IgA nephropathy, there are more than twenty control randomized studies, other than cited above. Although some of these studies were conducted on a small scale, they deserve a careful consideration and may help us draw valuable conclusions. In conclusion, it seems that IgA nephropathy and other glomerulopathies should be treated according to their severity and considering both the risk and benefits to individual patients.

Tadeusz Orłowski, a pioneer of the systematic approach to immunosuppressive therapy in glomerulopathies, believed that we should never stop searching for the best therapeutic approach based on a comprehensive and critical evaluation of current knowledge. His work and writings bear testimony to these principles.

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ARTYKUŁ POGLĄDOWY

Leczenie immunosupresyjne w kłębuszkowym zapaleniu nerek

Ważne osiągnięcie Tadeusza Orłowskiego i jego szkoły

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STRESZCZENIE

Pierwotne kłębuszkowe zapalenia nerek (KZN) są trzecią co do częstości przyczyną schyłkowej niewydolności nerek. Na początku lat sześćdziesiątych XX wieku Tadeusz Orłowski wprowadził w Polsce w sposób usystematyzowany leczenie immunosupresyjne KZN. Badania nad różnymi protokołami leczenia KZN prowadzone były w I Klinice Chorób Wewnętrznych (1962–1974) i w Instytucie Transplantologii Akademii Medycznej w Warszawie (1975–1990). Niniejsza praca w sposób krytyczny analizuje wyniki tych badań, szczególnie nad zastosowaniem skojarzonego leczenia immunosupresyjnego (prednizon/chlorambucil/azatiopryna) w różnych postaciach KZN. Pionierskie obserwacje poczynione w trakcie tych badań pozostają nadal aktualne. Leczenie immunosupresyjne w różnych schematach jest powszechnie przyjętą metodą leczenia KZN, szczególnie tych z zespołem nerczycowym, postępującym upośledzeniem czynności nerek i złym rokowaniem.

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