Pediatric Rheumatology

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Cyclophosphamide treatment with a comparison in both pediatric rheumatology and pediatric nephrology practices

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Abstract

Background Cyclophosphamide (CYC) is an inactive alkylating agent that transforms the alkyl radicals into other molecules and is used in combination with systemic corticosteroids in the treatment of many childhood rheumatic diseases, such as systemic lupus erythematosus (SLE), and ANCA-associated vasculitis (AAV). In recent years, rituximab (RTX), a B-cell-targeting anti-CD20 monoclonal antibody, has emerged as a new alternative treatment modality over CYC for induction therapy of childhood-onset rheumatic diseases. Clinicians adopt different practices for using CYC particularly in relation to indications, posology, pre-treatment laboratory work-up, post-treatment follow-up, and screening pre- and post-treatment vaccination status. This study aimed to evaluate the principles and approaches of administering CYC therapy in pediatric rheumatology and pediatric nephrology practices and to compare the clinician preferences for CYC and RTX in induction therapy of childhood-onset rheumatic diseases.

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Methods This study includes a web-based questionnaire executed on 87 participants (56 pediatric rheumatologists (PRs) and 31 pediatric nephrologists (PNs)). Both pediatric subspecialties evaluated and compared the most common indications for CYC treatment, pre-treatment consent protocols, pre-and post-treatment laboratory tests, dosing strategies, and side effects.

Results Childhood-onset SLE (95%) and AAV (69%) were the most common diseases for which CYC treatment is used. All clinicians, except 2 PNs prescribed CYC via intravenous route. 61% of the PRs and 71% of PNs reported using a monthly dose of 500 mg/m^2 CYC for 6 months in accordance with the National Institutes of Health (NIH) protocol. All clinicians conducted pre-CYC treatment assessments of complete blood count and kidney function tests. Hepatitis B (82%), chickenpox (76%), and mumps-measles-rubella (72%) were the most frequently assessed vaccines. Adverse effects associated with CYC include cytopenia (86%), nausea (52%), liver toxicity (20%), hair loss (31%), hemorrhagic cystitis (37%), allergic reactions (16%), dyspnea (5%), and infertility (2%). 9 clinicians stated that they performed gonad-sparing interventions before CYC, which clarifies why CYC was more commonly preferred in the induction therapy of SLE and AAV over RTX by both PRs and PNs.

Conclusions Clinicians still tend to choose CYC over RTX in induction therapy of SLE and AAV and mostly prefer the high-dose CYC treatment regimen suggested by the NIH.

Keywords Cyclophosphamide, Pediatric nephrology, Pediatric rheumatology, Rituximab, Side effects, Vaccination

Introduction

Cyclophosphamide (CYC) is an inactive alkylating agent that undergoes metabolic activation by cytochrome P450 enzymes in the liver, including CYP2A6, 2B6, 2C19, 2C9, 3A4, and 3A5, and then transforms the alkyl radicals inducing DNA damage, resulting in impaired cell division and apoptosis, to other molecules. Immunosuppressive and chemotherapeutic effects of CYC occur through the alkylation of bases by the stimulation of DNA injury, resulting in an effect on cell division and cell death, which may cause leukopenia, especially in T lymphocytes [1]. Since the 1980s, CYC therapy combined with corticosteroids has been widely used in pediatric rheumatology and pediatric nephrology practices as an induction treatment of childhood-onset systemic lupus erythematosus (SLE), systemic vasculitides, and pulmonary involvement of juvenile scleroderma, exhibiting varying success rates [2]. Lower doses of CYC are prescribed in rheumatological diseases compared to its use in the treatment of cancer chemotherapy. However, clinicians still have concerns about its long-term safety, especially the development of secondary malignancies and fertility problems due to CYC [3–5]. Apart from infertility, premature ovarian failure, and oncogenic risks, CYC treatment may have several side effects, such as leukopenia, gallbladder toxicity, and infection [3, 6, 7].

Cyclophosphamide is mainly used intravenously (IV), either 2 weeks apart or on a monthly basis, and is less frequently administered as a low-dose daily oral treatment [8]. IV CYC, coupled with hydration and uromitexan, are mainly preferred by clinicians to prevent bladder toxicity due to a reduced risk of bladder toxicity compared to oral CYC [9]. Infection risk is notably higher in SLE patients treated with CYC than in those treated with mycophenolate mofetil (MMF) or azathioprine [10]. However, there are no universally defined recommendations for performing routine laboratory tests before initiating CYC, especially screening complete blood count (CBC), because dose reduction may be required in patients with pre-existing leukopenia. The best monitoring time for leukopenia is approximately 10–14 days after the CYC treatment [11]. Additionally, screening vaccination cards and administering missing vaccines are essential for patients needing immunosuppressive treatments, including CYC [12]. Considering CYC's cumulative toxicity, infertility is an important side effect that becomes a strong concern for clinicians, patients, and caregivers regarding this old, effective, available, and cheap medicine [13]. Gonadotropin-releasing hormone (GnRH) analogues may prevent the development of premature ovarian failure in females, while sperm banking in males may be an alternative solution against this side effect [14, 15].

SLE is a multisystemic autoimmune disorder that may cause life-threatening organ involvement [16]. According to 2017 Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) recommendations, corticosteroids should be tapered as soon as possible, and hydroxychloroquine should be started for all childhood-onset SLE cases due to its steroid-sparing effect [17]. The 2023 EULAR SLE guideline recommended either CYC or MMF in combination with corticosteroids as induction therapy for proliferative lupus nephritis (class III and class IV) while using MMF or azathioprine for maintenance therapy [8]. The 2024 Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommended that in induction therapy, patients with active proliferative lupus nephritis (LN) should be given glucocorticoids plus one of the following regimens: (i) MMF; or (ii) low-dose IV CYC; or (iii) Belimumab and either MMF or

low-dose IV CYC; or (iv) MMF and a calcineurin inhibitor if the glomerular filtration rate (GFR) exceeds 45 ml/min per 1.73 m^2 [18]. The LN assessment with rituximab (LUNAR) trial showed that rituximab (RTX), a B cell targeting anti-CD20 monoclonal antibody, and MMF should be used as an alternative to CYC treatment in the induction therapy of LN [19]. Anti-neutrophilic cytoplasmic antibody (ANCA) associated vasculitis (AAV) is a small- and medium-sized vessel vasculitis that may cause multi-organ involvement comprising mild to severe life-threatening conditions [20]. American College Rheumatology (ACR) 2021 recommendations for the management of AAV induction treatment conditionally favoured high-dose corticosteroids in combination with RTX over CYC because of CYC-related toxicities, such as neutropenia, bladder toxicity, and infertility, which can be devastating for young patients. For refractory cases, ACR recommended switching from "CYC to RTX" or "RTX to CYC" instead of the concomitant use of CYC and RTX and stated that administering intravenous immunoglobulin (IVIG) should be useful [21]. However, as per 2024 KDIGO recommendations, AAV, RTX, and IV CYC could be prescribed together in severe cases [22]. This discrepancy between recent rheumatology and nephrology guidelines may be partly attributable to more severe kidney phenotypes in nephrology clinics. In recent years, RTX has been used as a new alternative treatment modality over CYC in induction therapy of SLE and AAV. Clinicians may prefer RTX over CYC because of concerns about its adverse effect profile [18, 22–24]. However, the widespread adoption of RTX is often challenged by its high treatment costs and low availability in most countries [25].

Clinicians embrace different practices for using CYC regarding indication, posology, pre-treatment laboratory work-up, side effects, post-treatment follow-up, and pre- and post-treatment vaccination status assessment [26, 27]. In addition, the preference rate of CYC treatment over new treatments by clinicians in pediatric rheumatology and nephrology clinical practices has yet to be evaluated. In this study, we aimed to assess and compare the use and preference of CYC in pediatric rheumatology and nephrology practices.

Materials and methods

This nationwide questionnaire study is designedto assess based on real-life experience with CYC usage in pediatric rheumatology and nephrology practices.

A web-based survey containing 33 questions about CYC use was created by two authors, one pediatric rheumatologist (PR) and one pediatric nephrologist (PN). The questions were organized in yes/no and multiple-choice formats. The questionnaire was sent via e-mail to pediatric rheumatology and pediatric nephrology specialists across Turkey. The first page of the questionnaire explained its theme and objective. In total, 280 clinicians with either PR or PN were invited to participate through the online questionnaire. 87 (31%) clinicians responded to the questionnaire, including 56 PRs and 31 PNs.

The study assessed multiple aspects like years of experience in the fields of pediatric rheumatology or pediatric nephrology, the number of patients treated with CYC therapy, the most common indication of CYC usage, and preference for using CYC as a maintenance or rescue treatment. Additionally, laboratory assessments and vaccination status pre- and post-treatment period, pregnancy tests, consent protocols for CYC treatment, the posology, dose intervals, and side effects of CYC were also examined, alongside preference between CYC and RTX in induction therapy. Supplementary material 1 shows the comprehensive questionnaire related to CYC seeking clinicians' responses.

The present study was approved by the Ethics Committee of the Gazi University (2024, approval number: 1362).

Statistical analysis

SPSS version 21 software (SPSS, Chicago, USA) was used to analyze the data. The categorical data were given as numbers and percentages. The distribution of the data was evaluated with the Shapiro-Wilks test. Differences between two independent groups were compared using an independent sample t-test for variables with normal distribution and the Mann-Whitney U test for variables without normal distribution. The characteristics of the groups were compared with Fisher's exact Chi-square test. A p-value less than 0.05 was considered as significant.

Results

87 pediatricians (56 PRs, 31 PNs) participated in the study. 14% of the PRs and 68% of the PNs have been working for more than 10 years in their respective subspecialty ($p < 0.001$) (Table 1).

Clinical experiences for CYC treatment

Table 1 illustrates the clinicians' clinical experiences. 23% of PRs and 32% of PN performed CYC treatment on more than 50 patients ($p = 0.359$). SLE and AAV were the most common indications for CYC induction therapy, respectively (Table 1).

CYC in SLE

CYC was reportedly prescribed in all lupus nephritis cases (class III and class IV) by both PNs and PRs. However, 93% of PRs and PNs prescribed CYC in neuro-lupus patients, compared to 16% of PRs and PNs who used it for other lupus-related indications. In CYC-resistant

Table 1 Cyclophosphamide experiences of the clinicians

	Pediatric rheumatologists	Pediatric nephrologists	*p*-value
	n **= 56 (100%)**	***n*** **= 31 (100%)**	
Professional experience of physicians			
1–3 years	10 (18%)	2 (6%)	0.139
4–6 years	20 (36%)	6 (19%)	0.110
7–10 years	16 (28%)	2 (6%)	*0.014*
>10 years	8 (14%)	21 (68%)	*< 0.001*
Number of CYC performed by physicians			
1–19 times	31 (55%)	14 (45%)	0.362
20–50 times	12 (21%)	7 (23%)	0.900
>50 times	13 (23%)	10 (32%)	0.359
The most common disease for which CYC is used			
SLE	55 (98%)	28 (90%)	0.092
AAV	42 (75%)	19 (61%)	0.180
In which disease is CYC therapy used for induction therapy?			
SLE	55 (98%)	28 (90%)	0.092
AAV	42 (75%)	18 (58%)	0.102
Takayasu arteritis	28 (50%)	2 (6%)	*< 0.001*
Systemic PAN	30 (54%)	4 (13%)	*< 0.001*
IgA vasculitis	4 (7%)	9 (29%)	*0.006*
Juvenile scleroderma	12 (21%)	1 (3%)	*0.022*
Juvenile dermatomyositis	15 (27%)	N/A	
IgG4 related disease	3 (5%)	1 (3%)	0.649
SRNS	N/A	9 (29%)	
SDRS	N/A	5 (16%)	
SDFRNS	N/A	6 (19%)	
SLE system involvement in which CYC is used			
Kidney (Class III and Class IV)	56 (100%)	31 (100%)	
Neurologic	52 (93%)	5 (16%)	*0.000*
Hematologic	17 (30%)	1 (3%)	*0.002*
Treatments used in CYC-resistant SLE			
Corticosteroids	56 (100%)	31 (100%)	
RTX	13 (23%)	5 (16%)	0.434
MMF	44 (79%)	19 (61%)	0.084
CSA or tacrolimus	1 (2%)	4 (13%)	*0.032*
IVIG	17 (30%)	4 (13%)	0.068
What agents do you use before CYC in SRNS?			
Pulse methylprednisolone/oral prednisolone	N/A	31 (100%)	
MMF	N/A	9 (29%)	
CSA or tacrolimus	N/A	17 (55%)	
Levamisole	N/A	5 (16%)	

CYC: cyclophosphamide; RTX: Rituximab; MMF: mycophenolate mofetil; CSA: cyclosporine A; IVIG: intravenous immune globulin; SLE: systemic lupus erythematosus; AAV: anti-neutrophilic cytoplasmic antibody-associated vasculitis; PAN: poly-arteritis nodosa; IgA: immunoglobulin A; SRNS: steroid-resistant nephrotic syndrome; SDNS: steroid-dependent nephrotic syndrome; SDFRNS: steroid-dependent frequently relapsing nephrotic syndrome; N/A: not available

patients with SLE, clinicians prescribed corticosteroids, MMF, RTX, and IVIG (Table 1).

CYC in AAV

75% of the PRs and 61% of PNs used CYC in induction therapy of AAV (Table 1).

CYC in nephrotic syndrome

35% of PNs preferred CYC in cases with steroid-dependent nephrotic syndrome (SDNS) or steroid-dependent frequently relapsing nephrotic syndrome (SDFRNS), while 29% preferred it for steroid-resistant nephrotic syndrome (SRNS) (Table 1).

Features of CYC administration

Features of CYC administration are summarised in Table 2. All clinicians, except 2 PNs, were prescribed CYC via IV route. Most clinicians stated to use 6 IV pulses of CYC at a dose of 500 mg/m² given one month apart. As reported by ¾ of the participants, the maximum IV pulse

Table 2 Posology of cyclophosphamide

	Pediatric rheumatologists	Pediatric nephrologists	*p*-value
	n **= 56 (100%)**	***n*** **= 31 (100%)**	
CYC route			
Oral	N/A	2 (6%)	
Intravenous	56 (100%)	29 (94%)	0.253
CYC dose			
500 mg/m^2 BSA	34 (61%)	22 (71%)	0.338
750 mg/m^2 BSA	N/A	2 (6%)	
1000 mg/m^2 BSA	22 (39%)	7 (23%)	0.113
Max CYC dose			
500 mg	3 (5%)	3 (10%)	0.446
750 mg	9 (16%)	3 (10%)	0.442
1000 mg	42 (75%)	22 (71%)	0.682
1500 mg	2 (4%)	2 (6%)	0.539
2000 mg	N/A	1 (3%)	
Number of CYC pulses in induction therapy?			
3	2 (4%)	5 (16%)	*0.039*
6	54 (96%)	26 (84%)	
The time interval between CYC pulses			
2 weeks	9 (16%)	5 (16%)	0.994
1 month	47 (84%)	26 (84%)	
Do you apply uromitexan together with CYC?			
Yes	55 (98%)	30 (97%)	0.667

CYC: cyclophosphamide; N/A: not available; BSA: body surface area

dose of CYC was 1000 mg, with a minimum of 500 mg. Almost all clinicians performed uromitexan therapy concomitantly with IV CYC to prevent hemorrhagic cystitis.

Preparations before CYC treatment

Preparations done by the clinicians before CYC are given in Table 3. Most clinicians check CBC, kidney function tests (KFTs), and urine specific gravity as routine tests before administering CYC treatment, while liver function tests (LFTs), acute phase reactants, and beta-human chorionic gonadotropin (HCG) were more commonly evaluated by PRs than PNs ($p = 0.032$, $p = 0.001$ and $p = 0.047$, respectively). About half of clinicians reported examining for pregnancy before CYC treatment. Only 9 clinicians, 8 PRs, and 1 PN, performed gonad-sparing interventions before CYC, including GnRH analogues and sperm preservation. All clinicians, except 3, screened the vaccine status of the patients before administering CYC. The most frequently screened vaccines were hepatitis B (HB), chickenpox, and measles, mumps, and rubella (MMR) vaccines, respectively. 50% of PRs and 35% of PNs administered CYC treatment 1 day after non-live vaccines ($p = 0.684$). However, 66% of PRs and 68% of PNs administered CYC treatment 1 month after live vaccines. When the tendency of physicians to administer vaccines to patients after CYC treatment was assessed, inactive vaccines were most frequently allowed after 1 month, while live vaccines were mostly allowed by PRs after 1 month (66%) and by PNs after 6 months (68%). PRs mostly preferred to check the CBC, LFTs, and KFTs within 1 to 2 weeks after administration of CYC, while PNs typically conducted these tests after 3 to 7 days.

Adverse effects related to CYC

Table 4 illustrates the adverse effects related to CYC based on participants' previous cumulative clinical experiences. The most common adverse effects associated with CYC were cytopenia (86%), nausea (52%), liver toxicity (20%), hair loss (31%), and hemorrhagic cystitis (37%), respectively. Hair loss was more commonly observed by PNs (48%) than PRs (21%) ($p = 0.009$). Additionally, 7–30 days after CYC treatment, approximately 40% developed a mild infection, and approximately 10% experienced a severe infection. PNs observed lower respiratory tract infections more frequently than PRs ($p = 0.032$).

The choice of induction therapy in SLE and ANCA-associated vasculitis: CYC vs. RTX

Both subspecialty experts stated that CYC should be prescribed more commonly as an induction agent in contrast to RTX (Fig. 1). In the presence of a life-threatening condition, 23% of the PRs and 16% of the PNs used CYC and RTX combination in induction treatment. Clinicians ranked the most critical factors in deciding between CYC and RTX for induction therapy as follows: efficacy, clinical experience of the drug, side effects, availability, patient age, cost, patient/caregiver's choice, ease of

Table 3 Preparations before cyclophosphamide treatment

	Pediatric rheumatologists	Pediatric nephrologists	*p*-value
	n **= 56 (100%)**	***n*** **= 31 (100%)**	
CYC pre-treatment assessments			
CBC	56 (100%)	31 (100%)	
Kidney function tests	56 (100%)	31 (100%)	
Liver function tests	55 (98%)	27 (87%)	*0.032*
Urine specific gravity	56 (100%)	29 (94%)	0.253
Acute phase reactants	41 (73%)	12 (39%)	*0.001*
Hepatitis markers	37 (66%)	19 (61%)	0.655
Viral serology	24 (43%)	9 (29%)	0.203
Beta HCG	13 (23%)	2 (6%)	*0.047*
2-way chest radiography	24 (43%)	13 (42%)	0.933
IGRA test	1 (2%)	N/A	
Electrocardiography	6 (11%)	N/A	
Pregnancy questioning before CYC treatment			
Yes	37 (66%)	14 (45%)	0.057
Gonad-sparing therapy before CYC treatment			
Yes	8 (14%)	1 (3%)	0.104
Which vaccines are questioned before CYC?			
Hepatitis B	46 (82%)	25 (81%)	0.862
Pneumococcus	28 (50%)	13 (42%)	0.470
Meningococcus	18 (32%)	9 (29%)	0.763
MMR	43 (77%)	20 (65%)	0.220
Chickenpox	44 (79%)	22 (71%)	0.427
Influenza	13 (23%)	4 (13%)	0.245
COVID-19	6 (11%)	4 (13%)	0.759
Not checking	2 (4%)	1 (3%)	0.932
Time to CYC administration after inactivated vaccine			
1 day	23 (50%)	11 (35%)	0.667
1 week	7 (13%)	1 (3%)	0.151
2 weeks	17 (30%)	9 (29%)	0.897
1 month	8 (14%)	8 (26%)	0.184
No idea	1 (2%)	1 (3%)	0.667
Time to CYC administration after live vaccine			
1 day	2 (4%)	N/A	
2 weeks	6 (11%)	1 (3%)	0.218
1 month	37 (66%)	21 (68%)	0.874
3 months	6 (11%)	8 (26%)	0.066
6 months	4 (7%)	N/A	
No idea	1 (2%)	1 (3%)	0.667
Time to inactivated vaccine after CYC administration			
1 day	13 (23%)	4 (13%)	0.172
1 week	5 (8%)	3 (10%)	0.907
2 weeks	15 (27%)	10 (32%)	0.589
1 month	22 (39%)	13 (42%)	0.058
No idea	1 (2%)	1 (3%)	0.667
Time to live vaccine after CYC administration			
1 month	37 (66%)	9 (29%)	*< 0.001*
6 months	18 (32%)	21 (68%)	*0.001*
No idea	1 (2%)	1 (3%)	0.667
How long after CYC do you check CBC?			
3 days	4 (7%)	9 (29%)	*0.006*
1 week	19 (34%)	12 (39%)	0.655
2 weeks	31 (55%)	9 (29%)	*0.018*

Table 3 (continued)

	Pediatric rheumatologists	Pediatric nephrologists	*p*-value
	n **= 56 (100%)**	***n*** **= 31 (100%)**	
1 month	2 (4%)	N/A	
I don't check	N/A	1 (3%)	
Do you obtain parental consent before CYC?			
Yes	41 (73%)	25 (81%)	0.437

CYC: cyclophosphamide; beta HCG: beta Human Chorionic Gonadotropin; CBC: complete blood count; N/A: not available; IGRA: interferon-gamma release assay

Table 4 Adverse events after cyclophosphamide treatment

	Pediatric rheumatologists	Pediatric nephrologists	*p*-value
	n **= 56 (100%)**	***n*** **= 31 (100%)**	
Adverse effects after CYC treatment			
Cytopenia	49 (88%)	26 (84%)	0.638
Nausea	27 (48%)	18 (58%)	0.378
Liver toxicity	11 (20%)	6 (19%)	0.974
Hair loss	12 (21%)	15 (48%)	*0.009*
Hemorrhagic cystitis	17 (30%)	15 (48%)	0.094
Allergic reaction	8 (14%)	6 (19%)	0.537
Dyspnea	4 (7%)	N/A	
Infertility	2 (4%)	N/A	
Mild infection	25 (45%)	12 (39%)	0.591
Severe infection	5 (9%)	3 (10%)	0.907
No adverse effects	1 (2%)	N/A	
How long after CYC did the infection develop?			
1 week	20 (36%)	8 (26%)	0.343
2 weeks	17 (30%)	8 (26%)	0.653
1 month	6 (11%)	4 (13%)	0.759
3 months	N/A	2 (6%)	
Infections after CYC			
Upper respiratory tract infection	31 (55%)	14 (45%)	0.362
Lower respiratory tract infection	10 (18%)	12 (39%)	*0.032*
Herpes simplex infection	7 (13%)	3 (10%)	0.835
Skin infection	3 (5%)	N/A	
Urinary tract infection	4 (7%)	2 (6%)	0.903
CMV infection	5 (9%)	N/A	
Pneumocystis jirovecii infection	2 (4%)	2 (6%)	0.539
COVID-19 infection	N/A	2 (6%)	
Opportunistic fungal infection	3 (5%)	3 (10%)	0.446
Influenza	3 (5%)	1 (3%)	0.649

CYC: cyclophosphamide; CMV: cytomegalovirus; N/A: not available

use of the drug, and disease severity, respectively. PNs were more concerned regarding access to medication ($p = 0.040$) (Table 5).

Discussion

This study entails a comparison between the approaches of PRs and PNs for using CYC treatment in their daily practices. Based on the statements of participating physicians, SLE and AAV are the most common diseases for which CYC treatment is used. CYC was often preferred by clinicians over RTX for induction treatment of severe organ involvement in SLE and AAV. Clinical experience, efficacy, and drug availability were the main reasons for choosing CYC over RTX treatment. Despite heterogeneity among treatment approaches adopted by clinicians, the most commonly utilized CYC posology included six doses, administered one month apart, coupled with IV 500 mg/m²/dose CYC with uromitexan. Before CYC treatment, all clinicians evaluated CBC and KFTs, and 80% of the clinicians checked vaccination status.

Our results showed a clear tendency of CYC over RTX in SLE and AAV induction treatment. Although SLE treatment guidelines do not include the combined use of CYC and RTX, this combination therapy showed efficacy in some refractory cases with childhood-onset SLE [28]. In our survey, 23% of PRs and 16% of PNs stated

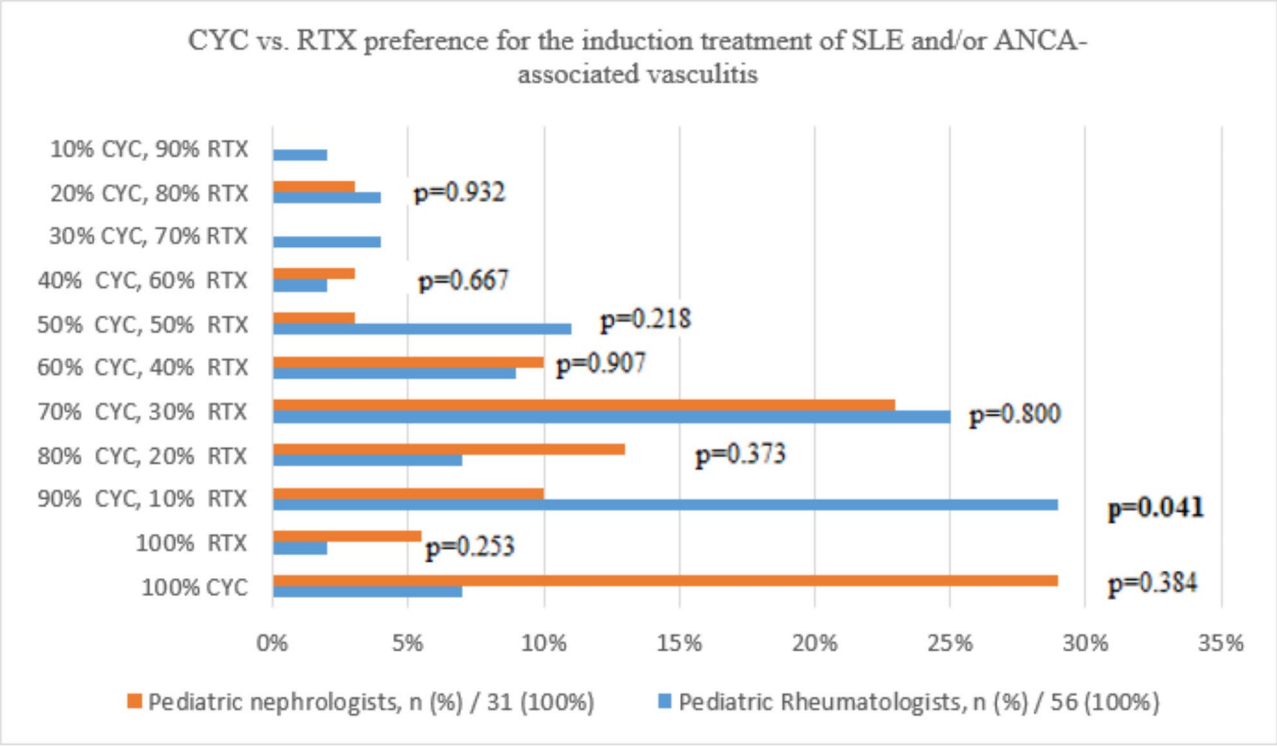

Fig. 1 Cyclophosphamide vs. rituximab
CYC: cyclophosphamide; RTX: Rituximab; SLE: systemic lupus erythematosus; AAV: anti-neutrophilic cytoplasmic antibody-associated vasculitis
Fig. 1 shows clinicians' responses when asked about their approximate preference for CYC or RTX as the first choice of SLE and/or AAV induction treatment

Table 5 Rituximab vs. cyclophosphamide in the treatment of SLE or AAV

	Pediatric rheumatologists	Pediatric nephrologists	*p*-value
	n **= 56 (100%)**	***n*** **= 31 (100%)**	
Would you use CYC and RTX together for induction therapy?			
Yes	13 (23%)	5 (16%)	0.360
What drives you to choose CYC or RTX for SLE or AAV?			
Clinical experience	36 (64%)	18 (58%)	0.566
Efficacy	37 (66%)	16 (52%)	0.185
Ease of use of the treatment	11 (20%)	8 (26%)	0.505
Side effect profile	32 (57%)	15 (48%)	0.432
Availability	27 (48%)	22 (71%)	*0.040*
Patient's age	24 (43%)	14 (45%)	0.835
Cost	17 (30%)	9 (29%)	0.897
Patient/caregiver choice	17 (30%)	6 (19%)	0.265
Disease severity	6 (11%)	6 (19%)	0.263

CYC: cyclophosphamide; RTX: Rituximab; SLE: systemic lupus erythematosus; AAV: anti-neutrophilic cytoplasmic antibody-associated vasculitis

that CYC and RTX can be administered concomitantly if there is a life-threatening organ involvement. The use of CYC as induction and/or rescue treatment has been reduced in the past decade due to the emergence of new treatment options such as RTX [29, 30]. Clinical experience (62%), efficacy (61%), and availability (56%) were the primary determinants in selecting the administration of CYC or RTX to the patients, followed by side effects (54%), patient's age (44%), and cost (30%). Interestingly, the ratio of physicians who considered disease severity as a key variable in the choice of CYC and RTX in induction treatment was only 14%. PNs were more concerned about the availability of drugs than rheumatologists ($p = 0.040$), which may be partly related to the relatively older history of the pediatric nephrology subspecialty in Türkiye, dating back to the 1980s when only CYC was available. This underscores the continued relevance of CYC as an old but effective, cheap, and easily accessible drug that may serve as a rescue treatment in refractory cases with chronic rheumatic and/or nephrological diseases.

There are different dosing recommendations for IV CYC usage [26, 27]. The National Institutes of Health (NIH) recommended a high-dose protocol as monthly 500–1000 mg/m²/dose [26], given 6 times one month apart, while the Euro-Lupus Nephritis Trial (ELNT) [27] proposed a lower-dose IV regimen of 500 mg/dose, administered 6 times 2 weeks apart [31]. In our study, the most preferred posology of IV CYC was monthly 500 mg/m²/dose, 6 times compatible with NIH recommendation, with a minimum of 500 mg and most commonly as a maximum of 1000 mg. The oral CYC regimen, 2 mg/kg per day for 3 months, may have more side effects than the IV regimen [6, 32]. Therefore, oral CYC may only be preferred if patients do not have easy access to an infusion centre and/or refuse IV therapy [18, 32]. In our survey, all clinicians except 2 PNs administered IV CYC to the patients instead of oral administration. NIH regimen recommended IV hydration and uromitexan alongside IV CYC to reduce bladder toxicity [26, 31]. In our survey, 98% of clinicians prescribed uromitexan during IV CYC treatment. A retrospective study from North America evaluating the effect of NIH and ELNT CYC protocols in patients with childhood-onset LN reported no significant differences in the achievement of renal response between the two regimens 12 months after CYC exposure [33]. In line with these findings, the low-dose CYC ELNT regimen appears safer than the high-dose NIH regimen [27, 31].

Several side effects might be observed after CYC treatment due to the potent immunosuppressive attributes [6]. In our survey, CYC-related emerged mostly after 1 to 2 weeks of CYC exposure. Cytopenia (86%), nausea (52%), infections (52%), hemorrhagic cystitis (37%), hair loss (31%), liver toxicity (20%), allergic reaction (16%), dyspnea (5%), and infertility (2%) were reported as most frequently observed complications. The most common infections after CYC exposure were upper respiratory tract infection (52%), followed by lower respiratory tract infection (25%), Herpes simplex virus (11%), Cytomegalovirus (6%), Pneumocystis jirovecii (5%), and opportunistic fungal infections (7%). However, it is worth acknowledging that patients with rheumatologic diseases treated with CYC also receive additional immunosuppressive therapies such as corticosteroids for a long time, which may further contribute to the risk of infection [18, 21, 22]. The risk of gonadal toxicity associated with cumulative doses of CYC is the main concern for both patients and clinicians [5, 6]. Silva et al. reported that 35 childhood-onset SLE patients (11%) who were treated with CYC developed premature ovarian syndrome [5]. On the other hand, Arici et al. described no differences in ovarian toxicity regarding cumulative CYC doses between patients with childhood-onset SLE who were CYC-exposure and CYC-naïve [34]. Owing to its impact on fertility, prospective studies with long-term observation are needed to clarify this issue in young patients. Anti-mullerian hormone (AMH) is a useful test for evaluating ovarian reserve [31]. Only 9 (10%) clinicians in our survey were performing gonad-sparing therapy before CYC administration, such as sperm preservation or GnRH analogues. Although these methods are expensive, the wide-spreading employment of gonad-sparing interventions can provide reassurance to both the physicians and the patients. Screening pregnancy in patients who will use CYC is essential [6]; 59% of the clinicians surveyed pregnancy, and 17% examined beta HCG levels before CYC exposure. 76% of the clinicians had consent from the caregiver for the treatment. There are no dosage adjustments before CYC treatment. The best monitoring time of CBC is 10–14 days after CYC exposure [11, 31]. Therefore, most clinicians in our survey tended to evaluate the CBC, KFTs, LFTs, urine density, acute phase reactants, and hepatitis markers before CYC therapy. PRs evaluated LFTs, acute phase reactants, and beta HCG levels more significantly than PNs. Most PNs perform laboratory tests one week after CYC exposure, while most PNs favoured assessments after two weeks.

There are no specific vaccination recommendations for patients treated with CYC. EULAR updated the vaccination recommendations for pediatric autoimmune inflammatory rheumatic diseases in 2021 [35]. All age-appropriate vaccinations should be performed on the patients before immunosuppressive treatment [12, 35]. In this study, most clinicians (40%) did not wait more than one day to prescribe CYC after any inactivated vaccine. However, if the patient met CYC exposure, most clinicians wait 2 weeks to one month to administer an inactivated vaccine. Non-live vaccines should be administered safely under immunosuppressive, whereas live-attenuated vaccines should be avoided. The MMR booster and varicella zoster vaccine should be applied to immunosuppressed patients in specific conditions [12, 35]. In our study, most clinicians (67%) waited 1 month after live vaccination to perform CYC unless there was a life-threatening condition. In live vaccine administration after CYC treatment, pediatric rheumatologists (66%) commonly waited 1 month, while pediatric nephrologists (68%) preferred to wait 6 months. Seasonal non-live influenza vaccination should be strongly recommended for patients with rheumatologic diseases [12, 35]. However, in our study, only 20% of the clinicians screened for the influenza vaccine before CYC exposure.

In conclusion, this is the first study evaluating PRs and PNs' approaches to CYC treatment in routine clinical practice. CYC therapy has been used safely for childhood rheumatologic and nephrologic diseases since the 1980s. Although, in recent years, the use of CYC has declined slightly due to the introduction of biological therapies

and concerns about side effects, clinicians still tend to choose CYC over RTX in induction therapy of SLE and AAV. The clinicians' approaches to using CYC regarding pre-treatment laboratory tests, monitoring of patients, and screening vaccination status show heterogeneity. Preparing pediatric guidelines, which include pediatric posology, routine tests, and vaccination before and after CYC exposure, can increase clinicians' awareness and improve patient care.

Abbreviations

ACR	American College Rheumatology
AMH	Anti-mullerian hormone
ANCA	Anti-neutrophilic cytoplasmic antibody
AAV	ANCA-associated vasculitis
CBC	Complete blood count
CYC	Cyclophosphamide
ELNT	Euro-Lupus Nephritis Trial
GFR	Glomerular filtration rate
GnRH	Gonadotropin-releasing hormone
HB	Hepatitis B
HCG	Human chorionic gonadotropin
IV	Intravenous
IVIG	Intravenous immunoglobulin
KDIGO	Kidney Disease: Improving Global Outcomes
KFTs	Kidney function tests
LFTs	Liver function tests
LN	Lupus nephritis
LUNAR	Lupus nephritis assessment with rituximab
MMF	Mycophenolate mofetil
MMR	Measles, mumps, and rubella
NIH	National Institutes of Health
PNs	Pediatric nephrologists
PRs	Pediatric rheumatologists
RTX	Rituximab
SDFRNS	Steroid-dependent frequently relapsing nephrotic syndrome
SDNS	Steroid-dependent nephrotic syndrome
SLE	Systemic lupus erythematosus
SRNS	Steroid-resistant nephrotic syndrome

Supplementary Information

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Supplementary Material 1

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Author contributions
DGY, EYO, CY, and SAB prepared the initial draft of the article. DGY, CA, HAD, OA, NA, EA, BNA, OAG, EAA, BA, POAA, FA, OB, EB, IB, KB, OB, USB, NB, BBY, BB, SC, MC, EC, FD, SD, YDY, FGD, ND, SD, ZET, EG, FH, RI, AK, MKC, UAA, HK, RMKE, ZK, TK, BK, EL, HN, GOY, SO, YOA, SOC, SPL, ES, HES, ENSY, SSD, SS, SS, AT, MT, SNT, BT, ST, ST, BUK, NY, KY, YT, ID, NC, SM, HP, RT, MKG, AB, YB, BAC, BS, EU, OK, and SAB contributed to the study conception and design. All authors contributed to data collection, analyses, and interpretation of data, providing comments on the draft article and final approval of the article. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval
This study was performed in line with the principles of the Declaration of Helsinki. The present study was approved by the Ethics Committee of the Gazi University (2024, approval number: 1362).

Consent for publication
Not applicable.

Consent to participate
All participants consented to participate in the survey study.

Competing interests
The authors declare no competing interests.

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