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Efficacy, Side Effects, and Monitoring of Oral Cyclosporine in Interstitial Cystitis/Bladder Pain Syndrome

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Abstract

Objective—To evaluate the efficacy of oral Cyclosporine A (CyA) in treatment of refractory interstitial cystitis/bladder pain syndrome (IC/BPS) and assess safety using drug level and renal function monitoring.

Methods—Patients with IC/BPS who failed at least 2 prior treatments were enrolled in an open-label study of oral CyA. Medication was started at 3 mg/kg divided twice daily for 3 months. Dose was adjusted based on side effects and drug level measured 2 hours after the morning dose (C2). Primary end point was marked or moderate improvement of global response assessment (GRA) or >50% improvement on the Interstitial Cystitis Symptom Index (ICSI) or Interstitial Cystitis Problem Index (ICPI) at 3 months.

Results—Twenty-two of 26 patients completed 3-month follow-up; 18 completed the post-study evaluation. Median symptom duration was 66 months (12–336). At 3 months 31%(8/26) improved by GRA, 15%(4/26) had >50% improvement in ICSI, 19% (5/26) in ICPI. Hunner's lesions (HL) predicted improvement in ICSI (OR=15.4; 95%CI:1.7–224.6, p=0.01) with 75%(3/4) of responders having HL. Two patients withdrew due to hypertension or elevated serum glucose. Mean nuclear glomerular filtration rate declined at 3 months (98.9±31.6 vs. 84.2±25.5 ml/min/

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1.73m2, $p=0.01$) and reversed to baseline after treatment discontinuation. C2 levels did not correlate with symptoms but allowed dose reduction in 11 patients.

Conclusions—Per AUA guidelines Cyclosporine A can be effective in a proportion of patients with refractory IC/BPS. Patients with HL are more likely to benefit. Monitoring of C2 rather than trough levels, can lead to dose reduction thereby minimizing toxicity.

Keywords

Interstitial Cystitis; Bladder Pain Syndrome; Hunner's Lesions; Cyclosporine

Introduction

IC/BPS affects 2.7% to 6.53% of the US population^{1, 2} and carries a significant financial burden, however effective treatments are lacking. Cyclosporine has been used extensively in the field of organ transplantation and has potent immunosuppressive properties. Cyclosporine binds calcineurin and inhibits NF- κ B thus blocking expression of T cell derived cytokines. Prior studies explored the use of cyclosporine in IC/BPS with excellent results^{3–5} and showed CyA to be superior to pentosan polysulfate⁶. These studies were small and heterogeneous. Patients were not phenotyped based on UPOINT^{7, 8} symptoms.

AUA guidelines propose the use of CyA as a fifth line therapy for IC/BPS⁹. Anecdotally, it is seldom used by urologists due to unfamiliarity with the drug monitoring and concern for potential side effects. Indeed, the pharmacokinetic properties and the side effect profile of cyclosporine are complex. CyA toxicity is correlated with drug levels¹⁰ and thus drug levels are commonly used for dose adjustment in organ transplantation. Close monitoring of the CyA levels is needed due to a narrow therapeutic index. In IC/BPS patients the CyA dosage used is low⁵ and risk of toxicity is decreased. Additionally, accuracy of drug monitoring has been recently improved by measuring the serum CyA level 2 hours after dose administration known as C2 level. The CyA area under the curve exposure is better approximated by the C2 level than the trough (C0)¹¹ and can minimize risk of drug toxicity. Thus we aim to increase urologist comfort with CyA use in IC/BPS by standardizing drug monitoring.

Nephrotoxicity of CyA is well-established side effect in organ transplant patients, however, most patients with IC/BPS have a normal starting creatinine and the effect on renal function may be less clear. Using creatinine alone to measure renal function may underestimate renal toxicity in a population starting with normal creatinine due to the shape of the creatinine/GFR curve¹². Direct GFR measurement can be helpful in understanding the change in GFR with CyA treatment and to evaluate if clinically significant changes are occurring with small changes in serum Cr. Isotope nuclear GFR using 125I-iothalamate provides an accurate and direct assessment of renal function and has been used in clinical studies to establish true GFR¹³.

The purpose of this study was to assess the safety and efficacy of low dose CyA treatment in patients with refractory IC/BPS. The secondary aim was to determine if treatment response is influenced by clinical factors and disease phenotype and to propose use of C2 levels, renal function, and blood pressure monitoring to minimize toxicity.

Materials and Methods

This is a single center open-label trial of CyA for treatment of patients with a clinical diagnosis of IC/BPS as defined by Society for Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction¹⁴. Patients 18–80 years of age with prior diagnosis of IC/BPS who failed at least 2 prior treatments and had an ICSI score of >9 were included. Male patients with IC/BPS had to have pelvic pain that was worsened with bladder filling and was relieved or improved with voiding¹⁵. Patients with active malignancy or history of urologic malignancy and/or bladder augmentation procedure, pelvic radiation, serum creatinine >1.5mg/dl, diabetes, untreated hypertension, proteinuria, recurrent urinary tract infections, spinal cord injury, or any patient on another immunosuppressive medication were excluded from the study. Patients who were using medications known to interact with CyA such as macrolide antibiotics, phenytoin, oral antifungals, and calcium channel blockers were excluded. Patients were identified in a tertiary referral center urology clinic from December 2013 to June 2015 and offered study participation. They were enrolled after they presented for a screening visit if they met all the criteria. The study was approved by the institutional review board (IRB #13-1271).

At the screening visit patients underwent clinical and laboratory evaluation, including establishment of UPOINT phenotype^{7, 8}, baseline serum creatinine levels and isotope nuclear GFR (Figure 1). All patients had a recent cystoscopy and presence of HL was recorded if noted. ICPI and ICSI screening tools were administered^{16–18}. After the screening visit patients were clinically evaluated at the start of the therapy and monthly for total of 3 months of therapy. Post study evaluation was done at 1–2 months after therapy was discontinued. Each patient was started on 3mg/kg CyA divided into two doses per day rounded to the nearest 50 mg. This is in contrast to the 5–10mg/kg divided into two doses per day in solid organ transplant recipient. CyA C2 level was used for drug monitoring and measured 2 hours after administration of the drug^{19–21}. At each follow up visit CyA levels, renal function, and blood pressures were monitored and dose was adjusted if side effects were noted or the CyA level was significantly elevated (>700 ng/ml). Nuclear GFR was obtained at baseline, at 3 months, and at a post-study visit.

At each follow up visit patients were evaluated with GRA²², ICPI and ICSI. Primary endpoint was moderate or marked improvement as evaluated by GRA at 3 months and/or >50% improvement in ICSI and ICPI scores (Figure 1). The number of dose adjustments was recorded and adverse events and side effects were monitored.

Results were presented as means and standard deviations or medians and ranges for continuous variables, and percentages and counts for categorical variables. Wilcoxon rank sum test was used to compare variables between groups at each time point or Wilcoxon signed rank for the same variables between time points. For both univariate and multivariable analysis, Firth's penalized-likelihood logistic regression was used to identify variables associated with improvement in ICSI and GRA and odds ratio (OR) and its 95% confidence interval were reported. Analyses were done using the statistical software package R (www.r-project.org) and all tests were considered significant with $p < 0.05$.

Results

From November 2013 to October 2015 26 patients were enrolled in the study. Eight patients referred for screening were excluded, as they did not meet all criteria. Median age of the study cohort was 52.5 years (26–74) and 54% (14/26) were female. The median duration of IC/BPS symptoms was 66 months (12–336), with 81% (21/26) of patients reporting 3 or more years of symptoms. Baseline characteristics of the cohort are described in Table 1. Notably, 27% (7/26) of patients did have HL on cystoscopy.

At the 3-month primary endpoint, data was available for 22 of the 26 patients. Four patients did not reach primary endpoint and withdrew from the study due to increasing pain, elevated blood pressure episode, lack of symptom improvement, and lack of transportation/time for follow up visit (Figure 1). Based on intention to treat analysis at 3 months 15% (4/26) of patients reported >50% improvement in ICSI scores. There was a mean decline in ICSI of 21%, ranging from 86% decline to 44% increase in scores with 54% (14/26) patients reporting some improvement. Overall ICSI scores dropped from a median of 15.0(9–19) at baseline to 12.0(2–19) at 3 months ($p < 0.01$) (Figure 2). ICPI scores were similar to ICSI, and 19% (5/26) patients reported >50% improvement with mean score decline of 23% (100% decline to 25% increase). ICPI scores dropped from a median of 14.0 (8–16) at baseline to 11.0 (0–16) at 3 months ($p < 0.01$) (Figure 2). Data was available for 18 patients at the post treatment visit at least 1 month after discontinuation of therapy. Median ICSI at post study visit remained unchanged from 3 months (11.0(1–19) vs. 12.0(2–19) respectively, $p = 0.65$) and 12% (3/26) of patients reported >50% improvement. ICPI data supported the ICSI with no statistically significant change in median raw value from 3 months to end of study 11.0 (0–16) vs. 11.0 (1–19) respectively ($p = 0.25$) (Figure 2). On GRA 35% (9/26) of patients noted marked or moderate improvement at 1 month, 35% (9/26) at 2 months, and 31% (8/26) at 3 months during treatment. Positive results persisted after CyA was stopped in half of the responders with 16% (4/26) reporting improvement after completion of the study (Figure 2).

One of the four patients with improvement in ICSI and ICPI scores did not improve based on GRA. However, all 8 patients who markedly or moderately improved by GRA at 3 months reported a positive change on ICPI ranging from 19% to 100% score improvement. Seven of the 8 patients also reported improvement on ICSI ranging from 33% to 86% improvement and one patient reported no change on ICSI.

Variables associated with improvement in GRA, ICSI, and ICPI symptoms were examined. On univariate analysis presence of HL was associated with >50% improvement in ICSI symptoms (OR=15.4; 95% CI: 1.7–224.6, $p = 0.01$), while gender, age, CyA levels, UPOINT phenotype, or duration of symptoms were not associated with improvement. Chronic narcotic use was not a barrier to improvement with CyA based on ICSI, ICPI or GRA. Thirty eight percent (3/8) of patients on narcotic pain medications improved by GRA at 3 months vs. 36% (5/14) ($p = 0.91$) of those not on narcotic medications. Gender did not predict response on ICSI, ICPI, or GRA - 63%(5/8) of responders on GRA were female vs. 50%(7/14), of non-responders ($p = 0.58$). Of the seven patients with HL 4 were female. Patients with HL showed higher rates of response to treatment with 42% (3/7) reporting

>50% improvement on ICSI vs. 11% (2/19) without HL. Similar results were noted with response on GRA and ICPI but these did not reach statistical significance - 57% (4/7) of patients with HL improved on GRA vs. only 19% (4/19) of those without HL (OR=9.0, 95% CI: 1.24–110; $p=0.03$) and 42% (3/7) had >50% improvement on ICPI vs. 11% (2/19) without HL (OR=11.3; 95% CI: 1.11–114.4, $p=0.04$).

CyA dose used was 3 mg/kg CyA divided into two doses per day rounded to the nearest 50 mg and total doses ranged from 150–300 mg/day at the start of the study. The median C2 level at initial dose was 710 ng/ml (124–1282) and with dose adjustments at the end of the study it was 412 ng/ml (70–1117). The final CyA dose ranged from 100–300 mg/day. C2 levels allowed dose reduction in 11 patients.

Blood pressures and kidney function were closely monitored throughout the study (Table 2). Two patients experienced side effects – one each with hypertension and elevated serum glucose. At 3 months there was a decline in renal function with treatment, which then improved back to baseline at the end of the study 1–2 months after drug discontinuation. Mean Cr changed from 0.93 ± 0.24 to 0.99 ± 0.27 ($p=0.08$) and calculated GFR changed from 80.5 ± 23.6 to 75.2 ± 22.1 ($p=0.07$) at 3 months and then improved to 0.91 ± 0.24 ($p=0.97$) and 81.3 ± 23.4 ($p=0.82$) respectively at post study visit (Figure 4). For the 20 patients who had nuclear GFR performed at 3 months mean nuclear GFR dropped from 98.9 ± 31.6 at baseline to 84.2 ± 25.5 ml/min/1.73m² at 3 months ($p=0.01$) but normalized at post study follow up to 97.2 ± 27.62 after CyA was discontinued ($p=0.89$).

Comment

IC/BPS has a subacute course and, while many patients find durable relief with standard therapies, others suffer from persistent or worsening symptoms and progress to surgical urinary diversion. CyA has been used in treatment of IC/BPS in several small open label studies and has been compared to pentosan polysulfate with promising results^{3–6}. Despite the weaknesses of the existing evidence, CyA was included in the AUA treatment guidelines as a fifth line therapy prior to proceeding to cystectomy and pain management⁹. In this study of a treatment resistant IC/BPS cohort about 30% reported moderate or marked improvement on GRA while 15% and 19% reported >50% improvement in ICSI and ICPI scores respectively after 3 months of therapy. While a modest proportion of patients improved, the criteria for improvement was strict and only patients who had marked or moderate improvement on GRA or >50% ICSI/ICPI improvement were considered to benefit. Overall 54% (14/26) reported decline in ICSI scores and thus other patients responded to treatment but to a lesser extent. Notably, not all patients with GRA improvement noted ICSI or ICPI improvement thus suggesting that patient's perception of benefit may be individualized.

After discontinuation of therapy about half of patients experienced continued symptoms improvement for a few months. The treatment effects may be long lasting rising a possibility for interrupted treatment regiments to minimize side effects. Longer follow-up is needed to determine the duration of medication effect and optimize treatment protocols.

Since the response rates to CyA in long standing IC/BPS are limited to a small proportion of patients physicians must weigh the risk-benefit ratio and manage patient expectations. It is valuable limit medication trial to patients who are most likely to benefit. This study examined patient characteristics in an attempt to identify the patients most likely to respond. The only predictive factor noted in literature has been the presence of HL⁵. In this study patients with HL were also most responsive to therapy, with 42% of patients with HL reporting >50% improvement in ICSI scores vs. 11% for patients without HL. This is in line with prior report of 85% improvement for patients with HL in a multicenter observational trial of 44 patients with IC⁵. Patients with HL may be more likely to respond to immunosuppressive effects of CyA because of pronounced active inflammatory changes present on bladder biopsy as compared to IC patients without HL²³. UPOINT phenotype was examined as a possible method of patient selection but was not predictive of treatment response in this patient cohort but this may be due to small sample size. Additionally, chronic narcotic use, a typical exclusion from clinical trials, was not a barrier to improvement with CyA and should not preclude providers from considering the medication in patients on chronic opioid medications.

One of the major reasons that CyA is reserved as fifth line therapy is because of potential side effects⁹. In this cohort 2 of the 26 patients withdrew secondary to side effects, which were hypertension and elevated serum glucose levels. Renal function is often affected by CyA and CyA can lead to renal failure at full immunosuppressive dose. In this cohort statistically significant decline in renal function based on serum creatinine, calculated GFR, and nuclear GFR was observed at 3 months of therapy and improved with discontinuation of therapy to original baseline. While statistically significant the difference was 7 points for calculated GFR and 15 points for nuclear GFR, which may be of limited clinical significance for a patient starting with normal renal function. Patients should however be fully counseled prior to treatment regarding a risk renal function decline which is reversible in the short term. Long term effect on renal function was not evaluated in this study and may or may not be reversible. Renal function should be monitored closely in patients on CyA therapy throughout the duration of treatment and drug discontinued or dosing adjusted if decline in renal function is noted. In a setting outside of a clinical trial the use of calculated GFR based on serum creatinine appears sufficient. The pharmacokinetics of CyA are complex and rely not only on patients' physiology such as weight, liver function but also can be altered by other medications. Dosing used for IC/BPS treatment is low compared to transplant patients with most studies using 1–3mg/kg/day^{3–5} however risks even at these doses are not negligible. The IC/BPS studies that monitored C0 levels rarely found them to be elevated. C2 is a superior measure of area under the curve exposure for CyA and its use in renal transplantation improves outcomes and limits toxicity²⁴. Using C2 levels along with monitoring of creatinine and blood pressures allowed dose reduction in 11 patients. C2 level is a superior technique to monitor CyA in IC/BPS patients and can allow providers to minimize toxicity and improve drug safety.

This study is limited by a small number of patients and lack of a placebo control group to demonstrate efficacy, although the benefit of CyA in this patient population has already been shown in a prospective randomized study⁴. To account for risk of placebo effect the outcomes measured were very conservative with >50% improvement on ICSI/ICPI or

moderate or marked improvement on GRA was considered as a positive response. Additionally, GRA and ICSI/ICPI evaluation at each time point may be confounded by patient recollection bias from month to month. While the symptoms may have significantly improved at 1 month, patient's perception of lack of change in symptoms from 1 month to 3 months may have resulted in lower GRA and ICSI scores at follow up.

This study demonstrates that toxicity profile of CyA is real but can be monitored and managed. Elevated blood pressure and creatinine were noted in the study and must be a component of clinical follow up for any patient on CyA therapy. Careful monitoring of the renal function is essential as renal function can decline during therapy. Along with blood pressure, it can be safely used as a tool to guide dose adjustment. C2 levels ranged widely and did not correlate with response to treatment. It is difficult to say if there is an optimal level to guide treatment, however C2 level was used to minimize the dose of the drug used and is a helpful and precise monitoring tool. Further, longer-term studies would be needed to evaluate how the proposed optimized dosing of CyA based on C2 levels affects long-term treatment outcomes and side effect profile.

Conclusions

We found that CyA can be effective in a proportion of patients who have failed multiple prior therapies however the known side effects of CyA may occur and can be significant if suitable monitoring and dose reduction are omitted. Patients with HL were more likely to respond to treatment however none of the other clinical factors predicted CyA response and chronic narcotic medication use did not preclude patients from having a response to CyA treatment. Side effects, including elevated blood pressure and decline in renal function, were noted and prompted dose reduction or drug cessation in a small number of patients. Drug level and toxicity monitoring remains an essential component of treatment. As with transplantation, C2 drug monitoring appeared to allow dose reduction without limiting efficacy and could be used in a clinical practice to minimize the risk of side effects.

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Figure 1.
Study Diagram.

Figure 2.
Mean ICSI, ICPI and GRA distribution outcomes at each visit.

Table 1

Cohort Baseline Characteristics

	Study Cohort (N=26)
Age (median, range)	52.5 (26–74)
Female	54% (14/26)
BMI (median, range)	28 (20–40)
Duration of symptoms (median, range)	66 (12–336)
Hunner's Ulcer	27% (7/26)
Narcotic Medication Use	31% (8/26)
Creatinine (mean, standard deviation)	0.93 ± 0.24
Nuclear GFR (mean, standard deviation)	80.5 ± 23.6
UPOINT	
U (Urinary)	100% (26/26)
P (Psychosocial)	38% (10/26)
O (Organ Specific)	100% (26/26)
I (Infection)	4% (1/26)
N (Neurologic/Systemic)	38% (10/26)
T (Tenderness)	69% (18/26)
ICSI (median, range)	15.0 (9–19)
ICPI (median, range)	14.0 (8–16)

Longitudinal study monitoring of renal function and blood pressure for all patients (mean and standard deviation).

Table 2

	Start (N=26)	1 Month (N=24)	2 Months (N=24)	3 Months (N=21)	Post Study (N=18)
Renal Function					
Creatinine	0.93 ± 0.24	1.02 ± 0.26	1.0 ± 0.24	0.99 ± 0.27	0.92 ± 0.23
Calculated GFR	80.5 ± 23.6	71.4 ± 19.9	71.3 ± 20.2	75.2 ± 22.1	80.0 ± 22.3
Blood Pressure					
Systolic	131 ± 17	132 ± 16	123 ± 23	133 ± 26	129 ± 18
Diastolic	74 ± 10	83 ± 10	79 ± 11	81 ± 10	74 ± 16