

Immunomodulatory Therapy for Chronic Tubulointerstitial Nephritis Associated Uveitis (TINU)

**Nicolette Gion MD,
Panagiota Stavrou FRCS
C. Stephen Foster MD, FACS**

ABSTRACT

Purpose: To describe the clinical course and treatment with immunomodulatory agents in patients with tubulointerstitial nephritis and uveitis (TINU) syndrome.

Methods: Retrospective analysis of the charts of 6 patients with TINU syndrome.

Results: The mean (\pm SD) age was 24.3 (\pm 16.5) years, range 13 to 49 years; four patients were children and two adults, three males and three females. Five of the six patients had anterior uveitis and one had panuveitis. All patients suffered several relapses despite treatment with topical, regional and oral steroids and methotrexate in one case. The introduction or modification of immunosuppressants (methotrexate, azathioprine or cyclosporin A) achieved control of the uveitis and prevented relapses over a mean (\pm SD) follow up period of 19.66 (\pm 10.01) months, range six to 34 months. No treatment-related side effects were observed.

Conclusions: TINU syndrome is a distinct disease entity in which the nephritis typically resolves, but the uveitis often becomes chronic and is treatment resistant. Immunomodulatory agents can achieve control of the inflammation and prevent relapses.

INTRODUCTION

Tubulointerstitial nephritis and uveitis (TINU) syndrome was first described in 1975 by Dobrin.¹ It is usually seen in children and young adults; females are affected more often than males.²⁻⁵ The nephritis usually precedes the uveitis, although simultaneous onset of both organs has been described.^{1,2,6} Patients usually present with systemic signs and symptoms including fatigue, malaise, anorexia, abdominal pain, fever and anemia. The acute renal failure is due to nephritis and typically resolves spontaneously or responds favorably to systemic steroid therapy.^{2,6-10} However, cases of nephrotic syndrome, relapsing nephritis and development of chronic renal failure, despite the use of systemic steroids and other immunosuppressants (chlorambucil and cyclophosphamide), have also been reported.¹¹⁻¹³ A few patients eventually require dialysis.^{14,15}

The uveitis of patients with TINU tends to be bilateral, anterior and non-granulomatous, and its course is usually relapsing. In most cases, topical steroids have been adequate in controlling the inflammation, while some patients require systemic steroid treatment.^{3,7,12,14,16-19} However, the follow-up in these reports has been relatively short and the long term visual prognosis in TINU patients is not well documented. A study with a relatively long follow-up time has shown that frequent relapses occur despite treatment with topical and/or systemic steroids.¹⁸ Steroid-resistant patients and those who exhibit recurrent attacks of uveitis after discontinuation of steroids pose a particular problem to the ophthalmologist.^{2,10,18,20} The purpose of this study was to describe the use of immunosuppressive agents in a group of patients with steroid-resistant TINU-syndrome.

PATIENTS AND METHODS

The charts of all patients with TINU seen by Dr. Foster between 1996 and 1999 were reviewed. Information regarding age, sex, race, renal biopsy results, interval between kidney and eye involvement, type of uveitis, topical and oral treatment for uveitis, visual acuity at presentation and at last examination, complications and follow-up were analyzed.

RESULTS

Six patients with TINU were included in the study. There were three male and three female patients; all were Caucasian. The mean (\pm SD) age was 24.3 (\pm 16.5) years, range 13 to 49 years. All patients presented with acute febrile illness associated with fatigue, malaise and nausea.

Laboratory investigations revealed high creatinine levels, proteinuria and anemia. The diagnosis of tubulointerstitial nephritis had been confirmed by renal biopsy in five of the six cases. These patients received oral steroids with normalization of renal function. The sixth patient gave a history of renal problems associated with high creatinine levels. Her renal function improved spontaneously.

Ocular involvement followed the nephritis in all but one patient, in whom both organs were involved simultaneously. The mean (\pm SD) interval between renal and ocular symptoms was 6.66 (\pm 6.64) months, range 0 to 14 months. All patients had bilateral, anterior uveitis apart from one patient, who initially presented with anterior uveitis which later evolved to panuveitis. Prior to referral to us, all patients had been treated with topical steroids, one with regional steroid injections, two with oral steroids and one with oral steroids and methotrexate. The patients were referred to our Service for evaluation and management because the uveitis had become chronic and relapsing at every attempt at discontinuation of treatment.

Examination in our clinic revealed bilateral non-granulomatous anterior uveitis in four patients, granulomatous anterior uveitis in one patient, and non-granulomatous panuveitis in another. The uveitis was complicated by posterior synechiae, elevated intraocular pressure (IOP), and cataract in two of the six patients. The IOP was controlled with topical hypotensives. Details of patient demographics and clinical features are shown in Table 1.

Laboratory abnormalities included mild anemia in all patients, positive antinuclear antibody (ANA) in one patient, elevated C-reactive protein (CRP) in one patient, elevated soluble interleukin 2 receptor (sIL-2R) levels in three patients, reduced total complement level in one patient, elevated C4 complement in one patient, positive Epstein-Barr virus IgG in one patient and elevated anticardiolipin-IgM in another one. Details of biochemical results are shown in Table 2. Analysis of HLA association in one patient showed HLA-A9, -A33, -B65 and \neg Cw8. A summary of previously reported HLA associations in TINU is given in Table 3.

Due to the previous history of relapsing uveitis despite treatment with topical and oral steroids, the relative risks and benefits of continued steroid therapy versus immunomodulatory treatment were discussed with the patients. Each was screened for risk factors which might preclude the use of certain immunosuppressive agents. Regular clinical evaluation according to disease activity and periodic complete hemograms, liver function tests, urinalysis, blood urea nitrogen (BUN) and serum creatinine were obtained in all patients before therapy and at 1 week to 6 weeks after initiating therapy.²¹ The frequency of this schedule was dependent on the particular agent used and its major potential toxicity. The mean (\pm SD) follow up time was 19.66 (\pm 10.01) months, range 6 to 34 months.

Oral methotrexate 7.5 mg/week was introduced in four patients, allowing discontinuation of steroid therapy without relapse of the uveitis. The methotrexate dose was adjusted to a maximum level of 12.5 mg/week, according to clinical response, patient tolerance and biochemical parameters. The uveitis was controlled on methotrexate in all four patients. Methotrexate was well tolerated, apart from abdominal pain seen in one patient (case 1), after increasing the dose from 7.5 mg/week to 10 mg/week. This resolved with a divided dose of 5 mg on two successive days per week. In another patient (case 3) the uveitis had not been controlled on subcutaneous injection of methotrexate 25 mg/week and oral prednisone 20 mg/day prior to referral to our Service. This patient had also developed iatrogenic Cushing's syndrome, elevated IOP and cataract. He responded well to cyclosporine A 5 mg/kg/day (400 mg/day) and azathioprine 3 mg/kg/day (250 mg/day). The sixth patient in this series (case 5) was advised to start oral methotrexate, but she chose to continue only on topical steroids, which were discontinued seven months later without relapse of inflammation over a follow-up period of one year. Two characteristic patients (cases 1 and 3) are presented in detail.

CASE REPORTS

Case 1

In 1997, a 13 year old girl developed an acute febrile illness associated with fatigue, thirst and nausea. Laboratory tests showed high creatinine levels and proteinuria, and clinical examination confirmed enlarged kidneys. Renal biopsy revealed tubulointerstitial nephritis (TIN). Normalization of the renal function was achieved quickly with systemic prednisone-therapy. Four months later,

and while the patient was still on prednisone, she complained of pain, redness and photophobia in both eyes. An ophthalmologist made the diagnosis of bilateral anterior granulomatous uveitis and treated her with 1% prednisolone acetate drops four times a day. The uveitis persisted for 11 months and recurred at each attempt at discontinuation of the topical steroid. Nine months later, the patient was referred to Dr. Foster.

On examination the visual acuities were 20/30, RE and 20/25 LE. There were some keratic precipitates in the LE and rare cells in the anterior chamber of both eyes. The fundus was normal in both eyes. Intraocular pressure was 13 mmHg, RE and 17 mmHg, LE. Results of laboratory studies showed a mild anemia and an elevated soluble interleukin 2 receptor (sIL-2R) level. The HLA-typing was positive for HLA-A9, -A33, -B65 and -Cw8.

After a discussion with the parents of relative risks and benefits of continued steroid therapy versus immunomodulatory treatment, the patient was begun on methotrexate, 7.5 mg/week and was advised to taper the topical steroids. Over the next 8 weeks, the methotrexate dose was increased to 10 mg/week due to recurrent uveitis with attempted steroid withdrawal. The patient responded well to this dose and remained free of relapses over a follow-up period of 7 months. On the latest follow-up examination the visual acuities were 20/25 both eyes and anterior chambers were quiet.

Case 3

A 13 year old boy had a history of acute interstitial nephritis, diagnosed by renal biopsy, which responded well to oral steroid treatment. Six months later, he developed painful red eyes and photophobia. The diagnosis of bilateral anterior non-granulomatous uveitis was made and he was treated with 1% prednisolone acetate drops four times a day. Because the uveitis did not respond to this treatment oral prednisone of 40 mg/day and subcutaneous methotrexate 25 mg/week were added. The patient had also developed high IOP, which was treated with timolol 0.5% twice daily and 0.5% apraclonidine three times daily. One year later, the uveitis was still active and the patient had developed side effects (cataract in the right eye and iatrogenic Cushing's syndrome). The patient was then referred to Dr. Foster for evaluation and management.

On examination in our clinic the patient's visual acuities were 20/20 in both eyes. There were 2+ cells in the anterior chamber of both eyes, 2+ cells in the vitreous of the right eye and the IOP was RE: 19 mmHg and LE: 23 mmHg. Laboratory tests showed mild anemia.

The relative risks and benefits of continued steroid treatment versus different types of immunomodulatory therapy were discussed with the parents and the patient was begun on cyclosporine A 5 mg/kg/day (400 mg/day) and azathioprine 3 mg/kg/day (250 mg/day), while the steroids were tapered. The patient suffered two mild recurrences of uveitis during the ensuing 34 months, which were treated by an increase in the dose of cyclosporine to 500 mg/day and continuation of the azathioprine dose. On last examination, the patient was still on the same treatment and had visual acuities of 20/25, RE and 20/16 LE, 10²+ cells in the anterior chamber of the right eye and no inflammation in the left eye. The IOP was under control on the initial hypotensive medication.

DISCUSSION

Acute interstitial nephritis (AIN) has a variety of etiologies, including drugs (antibiotics, diuretics, nonsteroidal antiinflammatory drugs), infections (viruses, group A streptococcus, pneumococcus, yersinia pseudotuberculosis, salmonella, legionella, mycobacteria, toxoplasma, leptospira) and immunologic disorders (sarcoidosis, Sjogren's syndrome, scleroderma, systemic lupus, Still's disease). AIN of unknown etiology is labeled idiopathic.^{2,13,22} The typical histological changes in human AIN consist primarily of interstitial edema and infiltration by lymphocytes, plasma cells, macrophages, eosinophils and neutrophils. Fibrosis is occasionally seen, but there are no glomerular changes present. These histological findings differentiate AIN from acute tubular necrosis.^{2,3,13} Uveitis has been reported in association with idiopathic TIN, and this syndrome, TINU, has been categorized as a separate clinical entity.

The pathogenesis of TINU-syndrome is not clear. Abnormalities of both humoral and cellular immunity have been reported, including antineutrophil cytoplasmic antibodies (ANCA),^{5,23-25} immune complexes in the aqueous⁷ and serum,^{6,26-29} elevated sIL-2R levels.^{6,23} elevated serum IgG1,^{11,18,27,29} and numerous CD4+, CD8+, CD11c+ cells in the interstitium of renal

biopsies.²³ Antibodies to chlamydia have also been reported in a 38 year old woman with TINU.³⁰ Various HLA associations have been described.^{18,20,23} In our series, abnormal findings included Epstein-Barr virus IgG, highly elevated anticardiolipin-IgM and increased C4 in one patient, ANA positivity and decreased total complement levels in another patient and elevated sII-2R levels in 3 patients. HLA-typing in one case showed HLA-A9, A33, -B65 and -Cw8.

Uveitis in TINU-syndrome is typically described as bilateral, anterior and non-granulomatous. However, patients with granulomatous uveitis and posterior segment involvement have also been reported.^{7,19,20,31} The uveitis tends to be recurrent, and relapses typically occur at discontinuation of treatment. The long-term clinical course of these patients is not well documented. In one study with a relatively long mean follow-up of 5.7 years, numerous relapses, despite topical or systemic steroid treatment, were described in 4 female patients.¹⁸ All of the patients presented here were referred to us because of recurrences of uveitis despite treatment with topical, regional and systemic steroids and (in one patient) methotrexate. Introduction or addition of immunosuppressants such as methotrexate, azathioprine or cyclosporine A in 5 of the 6 patients achieved control of the intraocular inflammation and prevented relapse during the follow-up period. Methotrexate alone (in 3 patients) and in combination with cyclosporin A (in one patient) was successful in controlling the uveitis. One patient (case 3) did not respond to the combination of methotrexate and systemic steroids and developed steroid-induced side-effects. He responded well to a combination of cyclosporin and azathioprine. All patients tolerated the chemotherapy well, apart from one patient (case 1) who complained of nausea and abdominal pain after taking methotrexate. These symptoms resolved after dividing the dose of methotrexate on two successive days.

Patients with recurrent anterior uveitis or posterior uveitis due to TINU have been treated with oral steroids with variable results. To our knowledge, the report by Sanchez et al²⁰ is the first one describing the use of steroid-sparing agents in the case of a patient with posterior uveitis in TINU-syndrome. The authors described several relapses of uveitis, despite the use of oral steroids, which persisted after addition of azathioprine. Their patient responded favorably to cyclosporin A as monotherapy.

The results of our analysis of the six cases presented herein confirm the prior observations that renal function generally normalizes quickly in patients with TINU, but the uveitis tends to be relapsing and can be treatment-resistant. Additionally, our case series confirms and extends the observation of Sanchez et al,²⁰ that the introduction of immunosuppressive treatment can achieve control of the intraocular inflammation and prevent relapses. Since no "best drug" is known for TINU syndrome, the selection of the most effective immunosuppressant must follow a "sequential stepladder approach," with low dose once weekly methotrexate generally being the first step, followed by cyclosporin A or azathioprine. As always, the use of such immunomodulatory therapy should be under the management of an individual who is, by virtue of training and experience, expert in such management.

REFERENCES

- Dobrin RS, Vernier RL, Fish AL. Acute eosinophilic interstitial nephritis and retinal failure with bone marrow-lymph node granulomas and anterior uveitis. A new syndrome. *Am J Med* 1975;59:325-333.
- Burnier M, Jaeger P, Campiche M, Wauters JP. Idiopathic acute interstitial nephritis and uveitis in the adult. *Am J Nephrol* 1986;6:312-315.
- Cacoub P, Deray G, LeHoang P, et al. Idiopathic acute interstitial nephritis associated with anterior uveitis in adults. *Clin Nephrol* 1989;31:307-310.
- Salu P, Stempels N, Vanden Houde K, Verbeelen D. Acute tubulointerstitial nephritis and uveitis syndrome in the elderly. *Br J Ophthalmol* 1990;7:3-55.
- Simon AH, Alves-Filho G, Ribeiro-Alves MA. Acute tubulointerstitial nephritis and uveitis with immune antineutrophil cytoplasmic antibody. *Am J Kidney Dis* 1996;28:124-127.
- Kindler J, Kemper R, Helmchen U. Acute tubulointerstitial nephritis and uveitis syndrome (TINU syndrome). Occurrence of uveitis after stopping steroids. *Nephrol Dial Transplant* 1998;13:1892-1893.
- Van Acker KJ, Buysens N, Neetens A, Lequesne M, Desmet N. Acute tubulointerstitial nephritis

and uveitis. *Acta Paediatr Belg* 1980;33:171-177.

Radig H, Bialasiwicz AA, Gerding H, Helmchen U. Tubulointerstitial nephritis and uveitis. *Ophthalmology* 1992;89:441-443.

Bunchman TE, Bloom JN. A syndrome of acute interstitial nephritis and anterior uveitis. *Pediatr Nephrol* 1993;7:520-522.

Rosenbaum JT. Bilateral anterior uveitis and interstitial nephritis. *Am J Ophthalmol* 1988;105:534-537.

Hausmann N, Neyer U, Haemmerle W. Akut rezidivierende Uveitis und idiopathische interstitielle nephritis – eine nosologische Einheit. *Klin Mbl Augenheilk* 1988;193:35-38.

Murray N, Wakefield D. Primary tubulointerstitial nephritis and uveitis syndrome. *Aus NZ J Ophthalmol* 1993;21:121-122.

Ellis D, Fried WA, Yunis EJ, Blau EB. Acute interstitial nephritis in children: a report of 13 cases and review of the literature. *Pediatrics* 1981;67:862-870.

Leumann EP, Nemeth J, Briner J. Akute interstitielle Nephritis und Uveitis: Ein neu erkanntes Krankheitsbild. *Schweiz Med Wschr* 1985;115:551-555.

Van Leusen R, Assmann KJ. Acute tubulointerstitial nephritis and uveitis and favorable outcomes after five months of continuous peritoneal dialyses (CAPD). *Neth J Med* 1988;33:133-139.

Rodriguez-Perez JC, Cruz-Alamo M, Perez-Aciego P, et al. Clinical and immune aspects of idiopathic acute tubulointerstitial nephritis and uveitis syndrome. *Am J Nephrol* 1995;15:386-391.

Hirano K, Tomino Y, Mikami H, et al. A case of acute tubulointerstitial nephritis and uveitis syndrome with a dramatic response to corticosteroid therapy. *Am J Nephrol* 1989;9:499-503.

Gafter U, Kalechman Y, Zevin D, et al. Tubulointerstitial nephritis and uveitis: association with suppressed cellular immunity. *Nephrol Dial Transplant* 1993;8:821-826.

Waeber M, Boven K, D°Heer B, Tassingnon MJ. Tubulointerstitial nephritis – uveitis (TINU)-syndrome with posterior uveitis. *Bull Soc Belge Ophthalmol* 1996;261:73-76.

Sanchez Roman J, Gonzalez Reina I, Castillo Palma MH, Rocha Castilla JL. Posterior uveitis associated with acute tubulointerstitial nephritis with favorable response to cyclosporin. Pathogenic implications. *Med Clin (Barc)* 1995;104:118.

Vitale AT, Foster CS. Immunosuppressive chemotherapy. In: *Textbook of Ocular Pharmacology*. Philadelphia: Lippincott-Raven 1997;723-726.

Morino M, Inami K, Kobayashi T, Yanagisawa K, Maeda K. Acute tubulointerstitial nephritis and uveitis in two siblings and concomitant uveitis in one. *Acta Paediatr Jpn* 1991;33:93-98.

Iitsuka T, Yamaguchi N, Kobayashi M, Nakamura H, Usuki J, Koyama H. HLA tissue types in patients with acute tubulointerstitial nephritis accompanying uveitis. *Nippon Jinzo Gakkai Shi* 1993;35:723-731.

Chen HU, Sheu MM, Tsai JH, Lai YH. Acute tubulointerstitial nephritis and uveitis with anti-neutrophil cytoplasmic antibodies in an adult: an autoimmune disorder? *Nephron* 1998;78:372.

Okada K, Okamoto Y, Kagami S, et al. Acute interstitial nephritis and uveitis with bone marrow granulomas and anti-neutrophil cytoplasmic antibodies. *Am J Nephrol* 1995;15:337-342.

Guesry P, Loirat C. Nephrite tubulo-interstitielle aigue et uveite. In: *Journées parisiennes de pédiatrie*. Paris: Flammarion 1976:187-197.

Iida H, Terada Y, Nishino A, Takata M, Mizumura J, Sugimoto T, et al. Acute interstitial nephritis with bone marrow granulomas and uveitis. *Nephron* 1985;40:108.

Vanhaesabrouck P, Carton D, DeBel C, Kalsow M, Yankelow JA, Organisciak T. Acute tubulointerstitial nephritis and uveitis syndrome. *Nephron* 1985;40:418.

Stupp R, Mihatsch MJ, Matter L, Streuli RA. Acute tubulo-interstitial nephritis with uveitis in a patient with serologic evidence for Chlamydia infection. *Klin Wochenschr* 1990;68:971-975.

Cavazza S, Molinari PP. Uveite intermediaire bilaterale et nephrite interstitielle aigue. Documentation echographique d°un cas. *J Fr Ophthalmol* 1994;17:59-61

Van Acker KJ. Acute interstitial nephritis and anterior uveitis. *Pediatric Nephrol* 1984;8:261-262.

Table 1. Patient Demographics and Clinical Features

No/Sex/Race	Age	Renal biopsy	Side	G / non-G	Uveitis type	Initial VA RE	Final VA RE	Systemic treatment	F-up (mos)	Complications
-------------	-----	--------------	------	-----------	--------------	---------------	-------------	--------------------	------------	---------------

						LE	LE			
1/F/C	13	yes	bilateral	G	anterior	20/30 20/25	20/25 20/25	MTX	23	Nil
2/M/C	14	yes	bilateral	non-G	panuveitis	20/30 20/80	20/20 20/20	MTX, CSA	26	elevated IOP, PS, cataract
3/M/C	13	yes	bilateral	non-G	anterior	20/20 20/20	20/25 20/16	1. MTX 2. CSA, AZA	34	elevated IOP, PS, cataract, Cushing
4/M/C	15	yes	bilateral	non-G	anterior	20/20 20/20	20/20 20/20	MTX	13	PS
5/F/C	49	no	bilateral	non-G	anterior	20/20 20/20	20/25 20/20	MTX advised	16	Nil
6/F/C	42	yes	bilateral	non-G	anterior	20/20 20/20	20/20 20/20	MTX	6	Nil

Treatment failure on methotrexate prior to referral to our Service; we switched therapy to cyclosporine and azathioprine.

VA: visual acuity, F: female, M: male, C: Caucasian, RE: right eye, LE: left eye, G: granulomatous, non-G: non-granulomatous,

F-up: follow-up, mos: months, MTX: Methotrexate, OS: oral steroids, CSA: Cyclosporin A, AZA: azathioprine,

TS: topical steroids, PS: posterior synechiae.

Table 2. Biochemical Studies

No/Sex	sIL-2R (U/ml)*	CRP (mg/dl)*	ANA-titer* (HEP 2 cell)	HB (g/dl) / HCT (%)	Other abnormalities*
1/F	890	<0.5	<1:40	12 38	Nil
2/M	Not performed	<0.5	<1:40	11.7 37.2	Nil
3/M	Not performed	<0.5	Not performed	11.3 35.4	Nil
4/M	1673	0.9	<1:40	12.6 33.6	TCL: 11 U/ml
5/F	1421	<0.5	1:160	10.7 31.3	Nil
6/F	688	<0.5	<1:40	9.7 29.6	EBV-IgG pos., aCL-IgM high, C4: 63 mg/dl

*sIL-2R: normal less than 820 U/ml, total complement level: normal range 20-40 U/ml, C4 complement: normal range 14-53 mg/dl,

CRP: normal range 0.0-0.5 mg/dl, ANA on HEP 2 cell: normal titer <1.40 homogenous pattern.

sIL-2R: soluble interleukin-2 receptor, CRP: C-reactive protein, ANA: antinuclear antibody, HB: Hemoglobin, HCT: Hematocrit,

EBV: Epstein Barr virus, aCL: anticardiolipin, TCL: total complement level.

Table 3. HLA-association

Author	Publication Year	No of Patients Tested	HLA-Type
Iitsuka T, et al ²³	1993	3 of 4	HLA-CW3

		4 of 4	HLA-A24
Gafter U, et al18	1993	4 of 4	HLA-DR6
Sanchez R, et al20	1995	1 of 1	HLA-A2, HLA-A23, HLA-B38, HLA-B44, HLA-DR6, HLA-DR7
Gion N, et al	1999	1 of 1	HLA-A9, HLA-A33, HLA-B65, HLA-Cw8