Clinical Kidney Journal, 2016, vol. 9, no. 2, 184–191

doi: 10.1093/ckj/sfv148
Advance Access Publication Date: 18 January 2016
Original Article

ORIGINAL ARTICLE

Outcome in patients with idiopathic retroperitoneal fibrosis treated with corticosteroid or tamoxifen monotherapy

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Abstract

Background: Although corticosteroids (CS) are used primarily in idiopathic retroperitoneal fibrosis (iRPF), tamoxifen (TMX) may be a suitable alternative. We compared outcome with CS or TMX monotherapy for first presentation in a large group of patients with iRPF disease.

Methods: Of all patients with iRPF disease who were seen at our tertiary care referral centre from February 1999 to December 2011, 118 patients were eligible for this retrospective study. Treatment success was defined as the composite of (i) amelioration of symptoms, (ii) computed tomography (CT)-documented mass regression and, if applicable, (iii) definitive removal of ureteral stent or nephrostomy tube. Recurrence was defined as recurrence of signs and symptoms and/or CT-documented mass increase after initial treatment success with primary treatment.

Results: Presenting signs and symptoms did not differ between patients treated with CS ($n = 50$) or TMX ($n = 68$). Time to amelioration of symptoms after treatment initiation was shorter in CS-treated patients [CS, 2.0 (0.8–3.8) weeks versus TMX, 4.0 (2.0–6.0) weeks; $P < 0.01$]. Short-term percentual decrease in acute-phase reactant levels ($P < 0.001$ for both erythrocyte sedimentation rate and C-reactive protein) and serum creatinine level ($P < 0.01$) following treatment initiation was greater in CS-treated patients compared with that in TMX-treated patients. Mass regression at first follow-up CT scan was observed more frequently in CS-treated patients (CS, 84.0% versus TMX, 68.3%; $P = 0.05$) with no difference in time interval from treatment initiation to first follow-up CT between groups [CS, 5 (2–7) months versus TMX, 4 (4–5) months; $P = 0.34$]. Definite treatment success was non-significantly higher in CS-treated patients (CS, 72.7% versus TMX, 58.3%; $P = 0.15$). In patients with initial treatment success with primary treatment, recurrence rate was lower in TMX-treated patients (CS, 62.5% versus TMX, 21.4%; $P < 0.01$).

Conclusions: CS are superior to TMX in treating iRPF disease. However, in patients with initial treatment success with primary treatment, recurrence rate was lower in TMX-treated patients.

Key words: corticosteroids, outcome, retroperitoneal fibrosis, tamoxifen, treatment

Received: August 26, 2015. **Accepted:** December 2, 2015

Clinical Kidney Journal

Introduction

Idiopathic retroperitoneal fibrosis (iRPF) is an uncommon disorder of unknown aetiology and characterized by the presence of a fibro-inflammatory tissue, which leads to fibrosis in the retroperitoneum. Typically, the fibrotic mass surrounds the abdominal aorta and the iliac arteries [1–3]. If left untreated, progressive disease leads to compression of retroperitoneal structures, notably the ureters.

With intelligent use of computed tomography (CT) or magnetic resonance imaging (MRI), a diagnosis of iRPF can be made with near certainty [1–5]. In case of diagnostic doubt, histologic confirmation of the presumed diagnosis should be sought.

Nowadays, medical treatment, if necessary with (urgent) renal drainage, is the preferred treatment strategy [1, 4, 6]. As auto-immune mechanisms are probably important in inducing the chronic inflammatory reaction [1, 4, 7, 8], corticosteroids (CS), either alone or combined with other immunosuppressants, are used most often as the primary treatment in iRPF disease [6, 9–16]. In recent years, tamoxifen (TMX) has been shown to be a viable treatment alternative with few side effects [4, 17–19]. The beneficial effects of TMX are probably hormone independent and based on its anti-inflammatory and antifibroblastic properties [17, 18]. To date, the ideal dosage, duration and comparative efficacy of different medical treatments are still unclear.

In this single-centre retrospective study, we compared treatment outcome in a large group of patients treated with initial high-dose CS or fixed-dose TMX monotherapy for first presentation of iRPF disease.

Materials and methods

Patients

For this retrospective study, all patients with RPF disease who were referred to our tertiary care referral centre for first or recurrent presentation between May 1991 and December 2011 were identified (Figure 1). RPF disease was considered idiopathic if the patient had a clinical and radiological diagnosis of RPF in the absence of any sign of malignancy and no history of infection or of taking drugs that could have been associated with RPF. We included patients with peri-aneurysmal fibrosis because this condition is also considered idiopathic [1, 2, 8, 20, 21]. Some patients with iRPF disease were excluded because of insufficient data (Figure 1). In 17 cases, the diagnosis was histologically confirmed. We were specifically interested in comparative outcome results of medical treatment with CS or TMX monotherapy for first presentation of iRPF disease. If medical treatment was initiated by the referring physician before referral or if the patient had a history of previous medical treatment for iRPF disease before referral, all medical records and abdominal CT scan images from the time of first presentation to referral were retrieved from the referring hospital. In those cases where CT scan images were not available, the radiological report was used [$n = 13$ (11%)]. Of iRPF patients who were included in an ongoing prospective observational study with TMX monotherapy for first or recurrent presentation at our centre, specific data from the time of first presentation were used for this retrospective comparative study. This study complied with the principles of the Declaration of Helsinki. The study was approved by our local ethics committee.

Treatment and follow-up

Choice of treatment regimen (i.e. drug, dose and duration) was at the discretion of the treating physician. All medical treatment and urological interventions for iRPF, particularly at the time of first presentation, were documented. Medications of interest were CS and TMX monotherapy. If no or another treatment was initiated at presentation of iRPF disease (i.e. other immunosuppressive agents or combined treatment including CS or TMX), patients were excluded from this study (Figure 1). For study patients treated primarily with CS, we recorded the initial starting dose (mg; mg/kg) and duration of this therapy (months). Study patients treated with TMX used a fixed dose (20 mg b.i.d.) for 2 years. Type of urological intervention (i.e. initial placement of ureteral stent or percutaneous nephrostomy tube) and time to subsequent definitive removal of the stent or tube were recorded. If performed, any other surgical intervention during the follow-up period (i.e. ureterolysis and aneurysmectomy) was recorded. In addition, we recorded the development of malignancy during follow-up and, if applicable, cause of death. A detailed history of specific treatment-related side effects was often not available, precluding such comparison, but any major adverse event that occurred during the follow-up was recorded.

Imaging results

All abdominal CT scans were independently reviewed. If performed elsewhere, we requested that the referring hospitals provide these CT images. The following variables from these imaging studies were assessed: localization of the soft tissue mass; the presence of extrinsic ureteral obstruction; the presence of hydroureteronephrosis (unilateral or bilateral and, if unilateral, which site was affected); the presence of renal atrophy (described as kidney length $\leq$8.5 cm); the presence of infrarenal aneurysmal aortic dilation, defined as aortic diameter $\geq$30 mm; and any other relevant intra-abdominal findings. During follow-up, CT-documented mass regression was categorized as follows: no regression, moderate regression (<50% mass reduction), significant regression (>50% mass reduction) and complete regression (no identifiable or measurable mass).

Measurements

Patient data on the following variables were abstracted: age, sex, medical history, smoking status (never, former or current), blood pressure, weight, length, date and time between onset of signs and symptoms and iRPF diagnosis. We registered the presence or absence of pain (abdominal, back and/or flank), weight loss, nausea or vomiting, constipation, fever, pollakisuria, leg oedema and claudication at the time of diagnosis. The presence or absence of subjective clinical improvement and time to amelioration of symptoms (weeks) as reported by the patient were also recorded. Baseline (i.e. at the time of first presentation) and follow-up laboratory measurements abstracted included complete white blood cell count (WBC), serum creatinine, albumin, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Because follow-up investigation in referring hospitals was at the discretion of the treating physician, analysis of short-term changes in laboratory values following treatment initiation at a specific time point was not possible. Therefore, to assess these short-term changes, we abstracted values of ESR, CRP and serum creatinine level when these were measured within a specific time period following initiation of medical treatment (i.e. between 4–6 weeks and 3–4 months, respectively). Primary outcome was treatment success. Treatment success was defined as the composite of three secondary end points, to be reached at completion of the primary treatment period: (i) amelioration of signs and symptoms; (ii) CT-documented mass regression; and, if applicable,

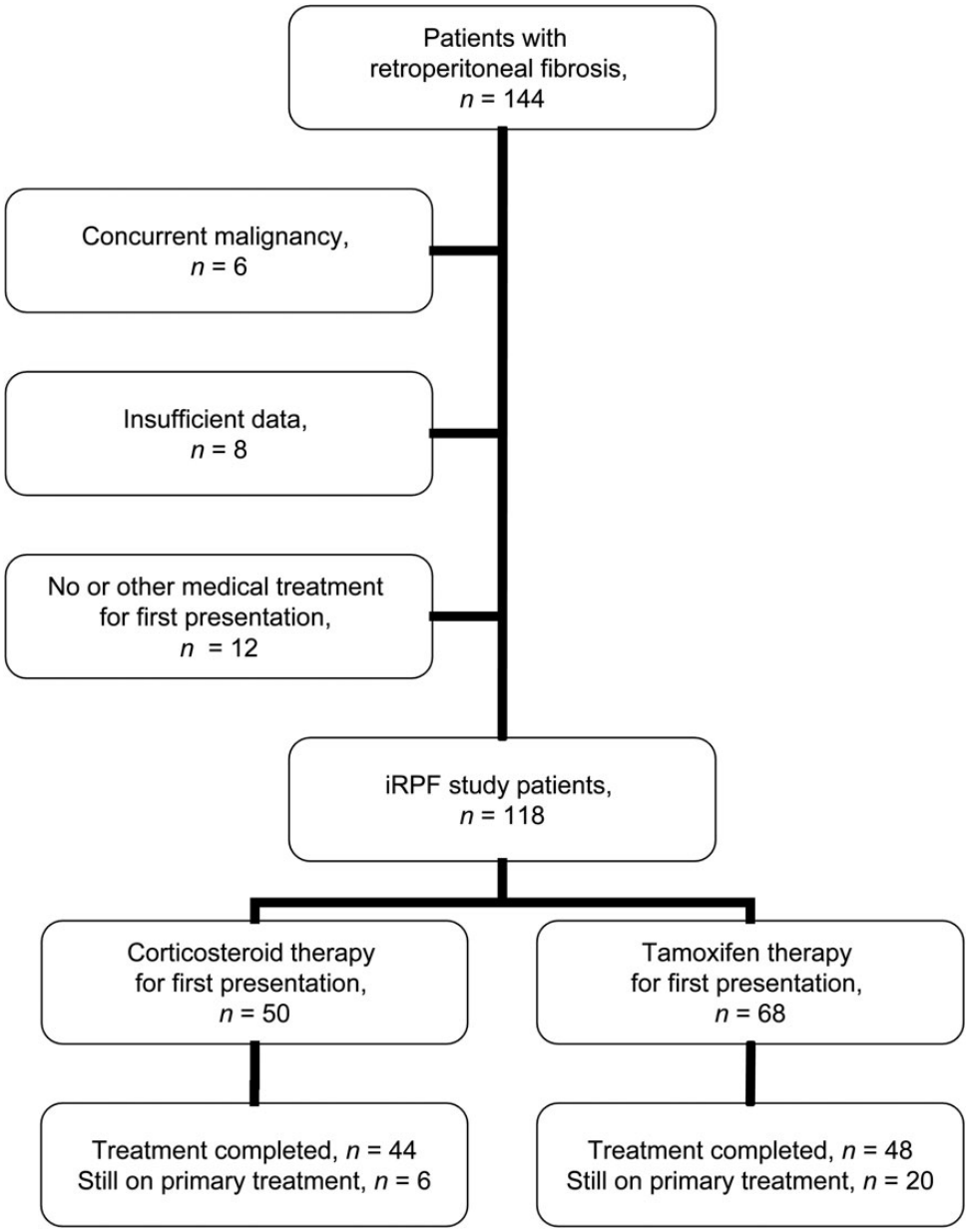

Fig. 1. Flow chart of patients through the study.

(iii) resolution of extrinsic ureteral obstruction, as defined by definite removal of the ureteral stent or nephrostomy tube. If the treating physician changed primary treatment because of unsatisfactory response (i.e. through addition of other immunosuppressive agents or conversion to other immunosuppressants), patients were considered to have had primary treatment failure. We did not consider (near) normalization of acute-phase reactant (APR) levels a prerequisite for treatment success as its meaning is unclear [22, 23]. Recurrences were defined as return of signs and symptoms after completion of successful primary treatment such that treatment was re-introduced.

Statistical analyses

Because many data were skewed, continuous variables were reported as median and 25th–75th percentiles (interquartile range, IQR). Differences between continuous variables were analysed using the Mann–Whitney or Wilcoxon matched pairs signed-rank test, where appropriate. Categorical variables were expressed as proportions and compared using Fisher's exact test. Spearman's rank correlation coefficient was used to test the correlation between APR levels, dose/duration of CS therapy, smoking history and current smoking with treatment success and recurrence rate. The Kaplan–Meier methodology with log-rank test was used to compare recurrence-free survival in patients with initial treatment success with CS or TMX. Recurrence-free survival in patients with treatment success was defined as time from discontinuation of medical treatment to recurrence. Reported P-values are two sided. A P-value of <0.05 was considered significant. All statistical analyses were performed with SPSS software (version 18.0; SPSS, Inc., Chicago, IL, USA).

Table 1. Demographic and clinical characteristics of study patients with idiopathic retroperitoneal fibrosis

		Primary treatment		
	Overall $n = 118$	CS, $n = 50$	TMX, $n = 68$	P-value
Age, years	58 (51–67)	55 (51–63)	59 (52–72)	0.05
Male sex, *n* (%)	81 (68.6)	34 (68.0)	47 (69.1)	0.90
Smoking,[a] *n* (%)	88 (74.6)	41 (82.0)	47 (69.1)	0.13
Hypertension, *n* (%)	40 (32)	13 (26)	27 (40)	0.17
Diabetes mellitus, *n* (%)	16 (14)	4 (8)	12 (18)	0.17
Cardiovascular disease[b]	23 (19)	7 (14)	16 (24)	0.24
Weight, kg	83 (70.5–90.9)	83 (69.8–90.5)	82 (71.0–91.6)	0.86
Body mass index, kg/m^2	26.6 (23.2–28.4)	26.0 (22.9–28.4)	26.8 (23.6–28.2)	0.75
Blood pressure, mmHg				
Systolic	145 (135–161)	145 (138–164)	147 (132–160)	0.86
Diastolic	85 (80–90)	85 (80–90)	85 (80–94)	0.65
Time from onset of symptoms to diagnosis, months	5 (3–8)	4 (2.5–6)	6 (2.5–10.5)	0.18
Aortic aneurysm,[c] *n* (%)	21 (17.8)	9 (18.0)	12 (17.6)	0.71
Hydroureteronephrosis, *n* (%)	67 (56.8)	28 (56.0)	39 (57.4)	0.61

Values are counts and percentage or median and IQR (25th–75th percentiles), where appropriate.
[a]Current or former smoker.
[b]Defined as coronary, peripheral vascular or cerebrovascular disease.
[c]Defined as infrarenal abdominal aortic diameter ≥3.0 cm.

Results

Our study population consisted of 118 patients (Figure 1). Fifty patients received CS therapy and 68 patients received TMX therapy as primary treatment for first presentation of iRPF disease. Median dosage of prednisone/prednisolone amounted to 60 (IQR 50–60) and 0.70 (IQR 0.61–0.86) mg/kg, respectively. All but two TMX-treated patients received 20 mg b.i.d.; the other two patients received 20 mg once-daily. TMX dosage per kilogram amounted to 0.49 (0.44–0.56) mg/kg. At the time of analysis, 6 patients in the CS group and 20 patients in the TMX group were still on primary treatment (Figure 1). TMX-treated patients were older then CS-treated patients, but otherwise there were no differences in demographic characteristics (Table 1). The percentage of patients with concomitant abdominal aortic aneurysm was similar in both groups. Time from onset of symptoms to diagnosis did not differ between groups (Table 1). Presenting signs and symptoms also did not differ between groups (Table 2). The most common presenting symptom was pain, often accompanied by significant weight loss, constitutional symptoms and constipation. Mean weight loss amounted to 8.36 kg, which did not differ between groups (CS, 7.0 kg versus TMX, 8.0 kg; P = 0.89). At presentation, patients receiving CS therapy had more increased APR levels and higher WBC compared with patients receiving TMX therapy (Table 3). Percentage of patients with uni- or bilateral hydroureteronephrosis at presentation and baseline serum creatinine level was similar in both groups. Forty-two patients (35.6%) received a percutaneous nephrostomy drain and/or (subsequent) double-J (D-J) catheter at first presentation, 18 (36.0%) in the CS group and 24 (35.3%) in the TMX group. After initiation of therapy, time to resolution of symptoms was shorter in CS-treated patients compared with TMX-treated patients (Table 4). Short-term percentual decrease in APR levels and serum creatinine level was greater in CS-treated patients compared with TMX-treated patients. CT-documented mass regression was observed more often at the first follow-up abdominal CT scan in patients receiving CS therapy compared with patients receiving TMX therapy. Time interval from the start of treatment to performance of the first follow-up CT scan did not differ between groups (Table 4). In 17 patients, the D-J catheter or nephrostomy drain was removed definitely at the end of initial therapy; four patients in whom the D-J splint could be removed were still on primary treatment. Median duration of stenting did not differ between groups [CS, 7 (IQR 4–15) months versus TMX, 8.5 (IQR 5.5–12.5) months, P = 0.95]. The percentage of patients who reached the aggregate end point of treatment success did not differ significantly between patient groups. In patients with initial treatment success with primary treatment, recurrence rate was lower in patients treated with TMX (Table 4). The Kaplan–Meier analysis for recurrence-free survival after initial treatment success showed better recurrence-free survival in TMX-treated patients (Figure 2). Post-treatment follow-up did not differ between groups (Figure 2). Baseline APR levels did not correlate with the aggregate end point of treatment success or recurrence rate in patients with initial treatment success in the overall group, or in the CS or TMX group (data not shown). Dose and duration of CS therapy did not correlate with the end point of treatment success or with

Table 2. Presenting signs and symptoms of study patients with idiopathic retroperitoneal fibrosis

		Primary treatment		
Signs and symptoms	Overall, $n = 118$	CS, $n = 50$	TMX, $n = 68$	P-value
Pain, *n* (%)	105 (89.0)	41 (82.0)	64 (94.1)	0.20
Abdominal	70 (66.7)	24 (58.5)	46 (71.9)	0.16
Back	59 (56.2)	26 (63.4)	33 (51.6)	0.23
Flank	44 (41.9)	15 (36.6)	29 (45.3)	0.38
Weight loss, *n* (%)	53 (44.9)	24 (48.0)	29 (42.6)	0.25
Constitutional symptoms, *n* (%)	72 (61.0)	28 (56.0)	44 (64.7)	0.78
Constipation, *n* (%)	31 (26.3)	13 (26.0)	18 (26.5)	0.76
Nausea or vomiting, *n* (%)	34 (28.8)	15 (30.0)	19 (27.9)	0.59
Fever, *n* (%)	18 (15.3)	10 (20.0)	8 (11.8)	0.11
Extremity oedema, *n* (%)	17 (14.4)	9 (18.0)	8 (11.8)	0.19
Claudication, *n* (%)	4 (3.4)	3 (6.0)	1 (1.5)	0.12
Pollakisuria, *n* (%)	25 (21.2)	9 (18.0)	16 (23.5)	0.96

the recurrence rate in patients with initial treatment success with CS therapy (data not shown). Neither smoking history nor current smoking correlated with TMX or CS treatment success (data not shown). During follow-up, surgical ureterolysis was performed in five patients [CS, $n = 4$ (8%) versus TMX, $n = 1$ (1.5%); P = 0.16]. At the end of follow-up, urine drainage was required in 20% of the CS-treated group and in 22% in the TMX-treated group (P = 0.82) because of newly onset or persistent hydroureteronephrosis. In both groups, only one patient reached end-stage renal disease during follow-up. Serum creatinine level did not differ between groups at the end of follow-up [CS, 95 (85–115) μmol/L versus TMX, 103 (77–156) μmol/L, P = 0.23] nor did the percentage of patients with impaired renal function (CS, 31% versus TMX, 44%; P = 0.20). During follow-up, major adverse events occurred in 27% of study patients (Table 5). Cardiac and infectious adverse events in the TMX group often occurred after conversion to second-line CS treatment, with or without added immunosuppressants, following TMX treatment failure (Table 5). The occurrence of a major event or intolerance of treatment led to dose tapering or interruption of treatment in seven patients (CS, $n = 5$; TMX, $n = 2$). Surgical aneurysmectomy was performed in two patients in the CS group and in two patients in the TMX group during follow-up. Seven patients (6%) developed a malignancy during follow-up (lung cancer, $n = 2$; colon carcinoma, $n = 1$; urothelial cell carcinoma, $n = 1$; liposarcoma, $n = 1$; melanoma, $n = 1$; Klatskin tumour, $n = 1$). Eleven patients died during follow-up, of whom five (10%) received CS therapy and six (8.8%) TMX therapy (P = 1.0) at presentation. No death was directly related to iRPF disease, but to malignancy ($n = 3$), cardiovascular disease ($n = 3$), infection ($n = 4$) or unknown cause ($n = 1$).

Table 3. Laboratory results at presentation in study patients with idiopathic retroperitoneal fibrosis

	Overall	Primary treatment		P-value
		CS, $n = 50$	TMX, $n = 50$	
ESR, mm/h	47 (26–84)	64 (40–95)	42 (15–79)	<0.01
CRP, mg/L	23 (7–54)	44 (16–99)	10 (5–34)	<0.001
WBC, $\times 10^9$/L	8.6 (6.8–10.1)	9.1 (7.8–11.1)	8.2 (6.7–9.4)	0.02
Haemoglobin, mmol/L	7.8 (7.2–8.7)	7.6 (6.9–8.5)	8.0 (7.3–8.8)	0.09
Albumin, g/L	39 (36–42)	38 (33–42)	40 (37–43)	0.06
Creatinine level, μmol/L	119 (92–155)	128 (90–205)	111 (92–141)	0.19

Values are median and IQR (25th–75th percentiles).
Hb, haemoglobin.

Discussion

Because of the rarity of the disease, treatment of iRPF disease has not yet been standardized and is largely empirical. Results of the present comparative study of CS and TMX monotherapy in a large group of patients with iRPF contribute to our knowledge of treating this uncommon disease. Patients who received CS monotherapy achieved more rapid resolution of clinical symptoms, a more rapid decrease in APR and serum creatinine levels, and more rapid radiological mass regression compared with patients receiving TMX monotherapy. Overall treatment success with CS monotherapy was also higher than with TMX monotherapy, although this difference was not statistically significant. Combined results confirm the superiority of CS to TMX. Despite its lesser efficacy compared with CS, our results also confirm that TMX is a suitable therapeutic alternative.

Table 4. Treatment outcome in study patients with idiopathic retroperitoneal fibrosis

Treatment outcome	Overall, ($n = 118$)	Primary treatment		P-value
		CS, $n = 50$	TMX, $n = 68$	
Amelioration of symptoms, week	3.0 (1.3–5.0)	2.0 (0.8–3.8)	4.0 (2.0–6.0)	<0.01
Short-term changes in APR levels, % (IQR)				
ΔESR after 4–6 weeks	58 (35–81)	88 (76–92)	42 (21–60)	<0.001
ΔESR after 3–4 months	66 (45–78)	75 (59–85)	62 (38–74)	0.01
ΔCRP after 4–6 weeks	54 (0–86)	83 (64–91)	38 (0–62)	<0.001
ΔCRP after 3–4 months	58 (0–83)	79 (55–90)	38 (0–75)	<0.01
Short-term changes in creatinine levels, % (IQR)				
ΔCreatinine after 4–6 weeks	1 (−8 to 24)	15 (−1 to 44)	−2 (−12 to 6)	<0.01
ΔCreatinine after 3–4 months	1 (−10 to 29)	28 (−3 to 54)	−2 (−11 to 12)	<0.01
Mass regression at first follow-up CT scan,[a] n (%)	85 (75.2)	42 (84.0)	43 (68.3)	0.05
Moderate regression, n (%)	43 (50.6)	16 (38.1)	27 (62.8)	
Significant regression, n (%)	30 (35.3)	20 (47.6)	10 (23.3)	
Complete regression, n (%)	12 (14.1)	6 (14.3)	6 (14.0)	
Time interval,[b] months	4 (4–6)	5 (2–7)	4 (4–5)	0.34
Treatment success,[c] n/total n (%)	59/92 (64.1)	31/44 (70.5)	28/48 (58.3)	0.23
Duration of therapy, months		14 (8–18)	24 (24–24)	
Recurrence, n/total n (%)	27/59 (45.8)	21/31 (67.7)	6/28 (21.4)	<0.01
Post-treatment follow-up, months		55 (23–122)	39 (19–50)	0.07

Values are counts and percentage or median and IQR (25th–75th percentiles), where appropriate.
[a]CT-documented mass regression was defined as follows: moderate, ≤50% reduction of mass; significant, >50% reduction of mass; complete, (near) complete regression of mass.
[b]Time interval from the start of treatment to first follow-up CT scan (months).
[c]Definite treatment success was defined as the aggregate of amelioration of symptoms, CT-documented mass regression and, if present, definite resolution of ureteral obstruction at the end of the primary treatment period. Patients who were still on primary treatment were not analysed for definite treatment success (Figure 1).

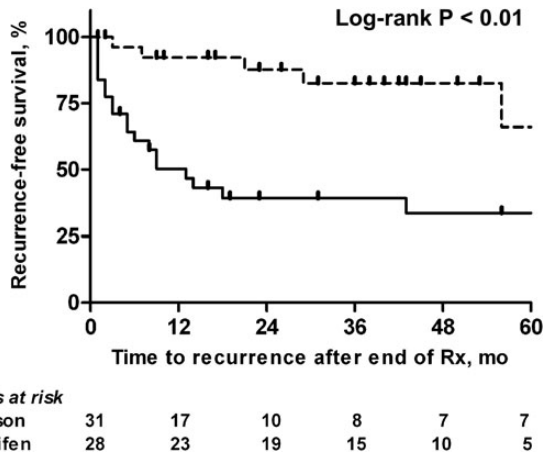

Fig. 2. Kaplan–Meier analysis of the time to recurrent active iRPF disease after discontinuation of primary treatment in patients with initial treatment success, showing better recurrence-free survival in patients receiving TMX treatment (dotted line) compared with patients receiving CS treatment (continuous line). Post-treatment follow-up did not differ significantly between groups [CS, 55 (IQR 23–122) months versus TMX, 39 (IQR 19–50) months; P = 0.07]. Patients were censored for end of follow-up or death.

Table 5. Major adverse events during follow-up in study patients

Adverse event	Overall, $n = 118$	Primary treatment: CS, $n = 50$	Primary treatment: TMX, $n = 68$
Patients with major adverse event,[a] *n* (%)	32 (27)	16 (32)	16 (24)
Severe infection, *n*			
Septicaemia[b]	6	1	5[c]
Severe pneumonia	1	1	
Ocular streptococcal infection	1		1[c]
Cardiovascular events, *n*			
Cardiac arrhythmias	7	3	4[c]
Acute coronary syndrome	6	1	5[c]
TIA/CVA	7	2	5
Thromboembolic events, *n*			
Deep vein thrombosis	3	2	1
Pulmonary embolism	4	3	1
Abdominal complications, *n*			
Recurrent peri-anal fistula/ abscess[d]	4	3	1
Perforated diverticulitis	1	1	
Perforated appendicitis	1	1	
Psychiatric disorders, *n*			
Depression	2	1	1
Psychosis	1	1	
Total number of adverse events, *n*	44	20	24

TIA, transient ischaemia attack; CVA, cerebrovascular accident.
[a]More than one major adverse event occurred in several patients.
[b]Typically (5/6) associated with (dysfunctioning) D-J catheter or nephrostomy tube *in situ*.
[c]The majority of infectious (5/6) and cardiac (5/9) adverse events occurred after conversion to second-line treatment (CS with or without added immunosuppressants) following TMX treatment failure.
[d]Requiring (repeated) surgical intervention.

To date, there is only one randomized, controlled trial in patients with iRPF disease [24]. In that study, all patients were initially treated with 1-month high-dose prednisone induction therapy. If remission was achieved, patients were randomly assigned to continue prednisone monotherapy ($n = 18$) or TMX monotherapy ($n = 18$) for a duration of 8 months. In this study, continuation of CS therapy was more effective in prevention of relapses than sequential treatment with CS and TMX [24]. This important study was the first to show superiority of CS therapy compared with sequential CS–TMX therapy. The relative contribution of TMX to mass regression, however, could not be assessed in this study as no radiological imaging was performed at the time of remission (i.e. at initiation of TMX therapy).

In a study evaluating the value of dynamic enhancement analysis of gadolinium MRI in the follow-up of 24 iRPF patients, some comparative outcome data of CS and TMX treatment were also reported [25]. In that study, frequency of MRI-documented mass regression at 6 months follow-up did not differ between patients receiving CS or TMX monotherapy (5/12 versus 8/12 patients). Frequency of definite removal of D-J stents at the end of 1-year treatment was also similar (CS, 7/12 patients versus TMX, 8/12 patients). Disease recurred in two CS-treated patients, 3 and 14 months after cessation of initial treatment, respectively [25].

In our study population, median duration of urine drainage amounted to 8 months, with no difference between patients treated with primary CS or TMX therapy. In addition, urine drainage was frequently still required at the end of follow-up in both treatment groups because of persistent or remitting ureteral obstruction. Treating physicians and patients should therefore be aware of the need for prolonged and/or repeated urine drainage with both therapies in many cases. Of note, short-term decrease in serum creatinine level was greater in CS-treated patients compared with TMX-treated patients, suggesting more rapid reversal of existing mild to moderate hydronephrosis in patients in whom urine drainage was considered unnecessary at presentation.

In the study by Vaglio *et al.* [24], better outcome with continued CS therapy compared with sequential CS–TMX therapy was seen at the cost of more side effects, notably cushingoid changes, greater weight gain and more frequent severe hypercholesterolaemia. Additionally, two patients had to stop prednisone because of intolerable side effects [24]. CS treatment in iRPF patients showed a high frequency of (transient) hyperglycaemia, hyperlipidaemia and aggravation of hypertension [11, 12, 14, 15, 26]. In one study, serious side effects attributable to CS use necessitating dose tapering or discontinuation of CS occurred in 21% of patients [12]. TMX is usually well tolerated with few side effects [17, 18]. The most frequent side effects included mood disturbances, hot flashes in women, fatigue, bone or muscle pain and, in men libido loss [17–19, 24]. The present comparative study did not allow a detailed assessment of specific side effects of both treatments. However, major adverse events were frequently noted in both groups, underlining the often compromised cardiovascular status of iRPF patients and the patient's increased susceptibility to infectious and thromboembolic complications.

In the present study, CS-treated patients had higher baseline APR levels compared with TMX-treated patients. We cannot readily explain this difference. It may be that higher baseline APR levels are thought to represent more intense (i.e. more 'active') iRPF disease by treating physicians, leading them to prefer CS therapy as the primary treatment. However, APR levels are poor predictors of a therapeutic response to CS and TMX [22, 23]. In the present study, duration of symptoms, presenting signs and symptoms and particularly frequency of hydroureteronephrosis

did not differ between patient groups. In addition, we observed no correlation of APR levels with treatment outcome in this study.

Optimal dose and duration of medical treatment are still unclear. Several approaches to medical treatment have been described and are mostly based on retrospective observational studies. To date, CS are the most used primary treatment. Reported success rates in CS-treated patients varies from 50 to 100% [4, 11, 12, 14–16, 26]. Our success rate of 70.5% falls within this range. The reported starting dose usually varied from 30 to 60 mg/day, with treatment duration varying from 6 months to 2 years [4, 11, 12, 14–16, 26]. Our patients received a median CS starting dose of 60 mg/day for a median duration of 14 months. Reported recurrence rates with CS treatment in other centres ranged from 9 to 44% [4, 11, 12, 14–16, 26]. In some studies, however, although reported as treatment success, several patients were still on low-dose CS maintenance treatment for up to 5 years, making evaluation of recurrence rate difficult [14, 15]. Despite initial high starting dose and usual duration of at least 12 months, we still observed a high recurrence rate in our CS-treated patients (67.7%), mostly within the first year after CS withdrawal. Therefore, a long treatment period seems advisable. Although we observed no correlation between CS dose or duration and treatment success, this may relate to the relatively small interpatient variability of dose and/or duration. Similarly, we observed no correlation between smoking and treatment response, which was observed by others [27].

Treatment success in our TMX-treated patients was 58.3%. Recurrence rate after TMX withdrawal in patients with treatment success amounted to 21.4%, which compared favourably to the recurrence rate in patients with initial CS treatment success. Although we acknowledge the superiority of CS, patients responding well to TMX also have a low recurrence rate. If used as primary treatment, these patients will not suffer from the potentially serious side effects of CS. In addition, TMX will not promote or mask tumour growth in cases where the retroperitoneal mass is caused by unrecognized malignant disease. In case of TMX treatment failure, subsequent second-line CS therapy is successful in the majority of cases [19]. Of note, the lower recurrence rate with TMX compared with CS may in part be explained by the much longer treatment duration of TMX therapy, further suggesting that a longer (low-dose maintenance) treatment period with CS seems advisable.

Several studies have demonstrated a typically increased cardiovascular risk profile in iRPF patients [2, 7, 10]. Demographic and clinical characteristics of our study patients confirmed this observation. In addition, cardiovascular events were observed frequently during follow-up. Long-term CS use accelerates the atherosclerotic process and increases the risk of cardiovascular morbidity and death [28]. Conversely, TMX may have cardioprotective effects [29, 30]. This may be particularly relevant when choosing the treatment regimen in patients with multiple cardiovascular risk factors (e.g. active smoking, diabetes mellitus and obesity) and/or established cardiovascular diseases (e.g. peri-aneurysmal fibrosis). TMX use is associated with an increased risk of venous thromboembolism (VTE) [31]. Although not readily recognized, CS use is also associated with an increased risk of VTE [32]. We observed thromboembolic events in both groups, which may also relate to the presence of pelvic venous compression by the retroperitoneal mass. Therefore, the risk–benefit ratio of both treatments should be carefully assessed in each patient with iRPF.

Because of the chronic relapsing course of iRPF disease, several reports have suggested the combination of CS or TMX with other immunomodulating agents such as azathioprine, methotrexate, cyclosporine and cyclophosphamide [6, 9, 10, 13, 27]. These regimens should be carefully weighed against the occurrence of potentially serious side effects, particularly cyclophosphamide [13]. More recently, high remission rates (72–89%) and low recurrence rates (0–7%) were observed with combined CS and mycophenolatemofetil (MMF) therapy [33–35]. These regimens usually included long-term use of MMF of up to 27 months with earlier CS withdrawal, usually after 6–7 months, thereby potentially lowering the risks of long-term CS use. However, its superiority to CS monotherapy is not yet clear, as no comparative data are available. To date, no data exist on MMF monotherapy in iRPF disease.

A major strength of the present study is the large number of patients included. To our knowledge, this is the first comparative study of these treatments on such a large patient group with iRPF disease with long-term follow-up. However, our study also has several limitations inherent to its retrospective design. There was no study protocol or randomization, and first-line treatment was at the discretion of the treating physician. As such, the patient's condition at presentation may have influenced treatment decisions. The possibility that treating physicians tend to start CS in a clinically more affected patient because time to resolution of symptoms is presumed to be shorter cannot be excluded. Although CT images were available from the majority of study patients, radiological results were sometimes extracted from the radiological reports. In addition, we could not assess and compare frequency and severity of specific treatment-related side effects, but we did record the occurrence of any major adverse event during follow-up.

In conclusion, initial high-dose CS therapy is more efficacious in achieving remission of iRPF disease compared with fixed-dose TMX therapy, as indicated by more rapid resolution of clinical symptoms, more rapid decrease in APR and serum creatinine levels and more rapid radiological mass regression. Overall treatment success with CS monotherapy was also higher than that with TMX monotherapy, although this difference was not statistically significant. Combined results confirm the superiority of CS over TMX therapy. Despite its lesser efficacy compared with CS, our results also confirm that TMX is a suitable therapeutic alternative. Therefore, the risk–benefit ratio of both treatments should be carefully assessed in each patient with iRPF disease.

Conflict of interest statement

None declared.

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