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# Usefulness of methotrexate in relapsing idiopathic retroperitoneal fibrosis

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## ABSTRACT

**Objective**. *Glucocorticoids are the mainstay for treatment of retroperitoneal fibrosis (RPF), a disease characterised by a periaortic proliferation of fibroinflammatory tissue frequently causing urinary obstruction. The therapeutic approach to patients unsuitable for steroid therapy and to relapsing cases is still undefined.*

**Methods**. *In this retrospective single-centre study we evaluated 15 patients with RPF who received second-line therapy with methotrexate (MTX) between January 2011 to December 2019.*

**Results**. *Fourteen out of 15 patients (93%) showed response to MTX. Two patients experienced relapse: one patient when on MTX therapy (28 months), the other, 58 months after MTX was interrupted. Liver toxicity grade 2 was documented in 2 patients and resolved with temporary dosage reduction. One patient stopped MTX autonomously because of nausea. No severe infections were recorded.*

**Conclusion**. *In selected patients with RPF who are intolerant or refractory to steroid single therapy, MTX may be considered as useful and safe second-line treatment.*

## Introduction

Retroperitoneal fibrosis (RPF) is a rare condition characterised by the development of fibro-inflammatory tissue in the retroperitoneum, which is frequently responsible for urinary tract obstruction (1). RPF may be primary (idiopathic) or secondary, with the idiopathic form accounting for 70 percent of cases and further distinguished in IgG4 or non IgG4-related (2).

Typically, patients present with flank or abdominal pain, in association with newly detected kidney function impairment and evidence of retroperitoneal fibrous tissue at imaging, although in some cases the diagnosis is incidental following radiologic studies (3-5).

The goals of therapy are to relieve pain and urinary obstruction, stop the progression, and prevent recurrence of RPF. Glucocorticoids are the mainstay of therapy for idiopathic RPF as they are effective in the majority of patients with response rates ranging from 75 to 90 percent (1 6). The approach to patients who fail or are not candidate to first line therapy with steroid is not well defined. Data on the use of methotrexate, mycophenolate mofetil, azathioprine and rituximab in RPF are available, yet based on small cohorts of patients or case reports (7).

In this retrospective study we aimed to describe the outcome of patients who received methotrexate for refractory or relapsing idiopathic RPF. Published experiences with immunosuppressive therapy in this setting were also reviewed.

## Materials and methods

We reviewed the clinical records of patients with a diagnosis of RPF followed at our care centre between January 2011 to December 2019. All patients gave informed consent before data collection. RPF disease was considered idiopathic in patients with characteristic clinical and radiological features of RPF, no sign of retroperitoneal malignancy, no extra-retroperitoneal manifestations, no history of hidden infection nor treatment with drugs potentially associated with the development of RPF. Patients with peri-aneurysmal fibrosis were considered as idiopathic. Response was evaluated by improvement of inflammatory indexes (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP] level, and serum creatinine concentration, and by computed tomography [CT] or magnetic resonance imaging [MRI]. Response was defined as mass reduction, absence of disease-related symptoms and normalisation of inflammatory markers (8). Relapse was defined in case of recurrent mass enlargement, hydronephrosis, or disease-related symptoms associated with elevation of inflammatory markers.

## Results

Sixty-four patients were considered for the study (median age 61, range 36–83; male n=42). All patients underwent CT or MR scans at diagnosis and 61 of them were further evaluated by positron emission tomography (PET)/CT) or PET/MR. Three patients underwent CT–guided percutaneous retroperitoneal biopsy. Following resolution of

**Table I.** Clinical characteristics of patients treated with MTX.

| | Gender | Age | Associated diseases | IgG4^ mg/mL | ESR-CRP* at diagnosis | Creatinine at diagnosis mg/mL | Ureteral obstruction at diagnosis | First line therapy (duration, weeks) | Reason for 2nd line | Duration of MTX therapy (months) | Follow-up from end of MTX (months) | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 44 | HP | 13.9 | 91 – 45 | Normal | No | PDN (44) | RL | 40 | 23 | R |
| 2 | F | 63 | Uterine leiomyoma | 201 | 65 – 38 | Normal | No | PDN (62) | RL | 30 | 88 | RL |
| 3 | M | 49 | CAD, HP | NA | 77 – 48 | Normal | Yes | PDN (15) | RF | 14 | 42 | R |
| 4 | M | 60 | AA, diabetes | 71.7 | 24 – 1.3 | Normal | No | PDN/TAM (13) | RF | 11 | 28 | R |
| 5 | M | 63 | Lung cancer | 62 | 11 – 2 | 7.2 | Yes | PDN (38) | RL | 18 | 38 | R |
| 6 | M | 65 | AA, HP, DL, BPCO | 27.8 | 5 – 1.2 | 5.9 | Yes | PDN (82) | RL | 22 | 32 | R |
| 7 | M | 61 | DL | 72.2 | 29 – 4 | Normal | No | TAM/PDN (8) | SSE | 35 | 50 | R |
| 8 | F | 50 | Lung cancer | 95.3 | n.a. – 2.8 | 6 | Yes | PDN (36) | RL | 28 | 44 | RL |
| 9 | M | 65 | CAD, HP, diabetes | 107 | 45 – 19 | 4.4 | Yes | PDN/TAM (10) | SSE | 10 | 46 | R |
| 10 | M | 48 | AA | 44.2 | 95 – 34 | Normal | Yes | PDN (18) | RF | 20 | 94 | R |
| 11 | M | 36 | DL | 74,5 | 12 – 3-2 | Normal | No | PDN (64) | RL | 19 | 90 | R |
| 12 | M | 53 | HP, DL | 63.5 | n.a. – 33 | Normal | Yes | PDN (16) | RL | 15 | 55 | R |
| 13 | M | 48 | Diabetes | 65.3 | 56 – 52 | 2.2 | No | PDN (10) | SSE | 4 | 63 | RF |
| 14 | F | 55 | Asthma | NA | 44 – 25 | Normal | Yes | PDN (22) | RL | 20 | 56 | R |
| 15 | M | 48 | None | 169 | n.a. – 3.3 | 5.30 | Yes | PDN (39) | RF | 36 | 5 | R |

AA: aortic aneurism (at RPF diagnosis); CAD: coronary artery disease; DL: dyslipidaemia; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HP: hypertension; NA: not available; MTX: methotrexate; PDN: prednisone; TAM: tamoxifene; R: remission; RF: refractory; RL: relapse; SSE: steroid side-effects.

^ serum IgG4 upper limit of normal: 135 mg/dL; * ESR normal values: 2–37; CRP normal values: 0–5 mg/L.

clinical symptoms and stabilisation of ureteral obstruction, if present at diagnosis, all patients underwent PET/CT or PET/MR by 6 months from diagnosis to evaluate response to first line therapy (median 17 weeks, range). The follow-up period ranged from 20 to 142 months (median, 78.5±39 months). Patients who were considered as responders to treatment were then clinically and laboratory assessed every 3–6 months. Patients who had ureteral obstruction at diagnosis were also checked by ultrasound examination at least every 6 months. Imaging evaluation to second line therapy was performed by PET/CT or PET/MR by 3 months from treatment initiation.

First-line therapy was prednisone alone in 50 patients, prednisone and tamoxifene in 11 patients, tamoxifene alone in 3 patients. All patients received steroids at 0.8–1 mg/kg for 4–8 weeks before tapering. Forty-four steroid-sensitive patients received steroid at a median duration of 8.4 months (range 6.4–11.5) showing stable remission at the follow-up (68.2%). Three patients were lost at follow-up (6, 8 and 12 months) when in remission following steroid suspension. Three patients relapsed following steroid discontinuation, one of them received azathioprine and steroids and 2 of them were treated with mycophenolate mofetil and steroids, obtaining clinical and laboratory remission.

Following first line therapy, 15 patients (3 patients refractory to steroids, 9 patients relapsing after steroids, 3 patients as adjunctive immunosuppressive therapy for relative contraindications to steroids) received weekly oral methotrexate (MTX), at the dose of 7.5–15 mg (median 12.5 mg). All patients had an estimated glomerular filtration rate (eGFR)>50 ml/min. Clinical details are shown in Table I.

Fourteen out of 15 patients (93.7%) showed response to MTX. Six patients (no. 2-7-8-10-11-15) showed mass reduction with persistent but reduced PET-positivity. Five patients (no. 5-6-9-12-14) showed mass reduction and complete resolution of metabolic activity. In three patients, complete mass regression was observed (no. 1-3-4). One patient (no. 13) had treatment failure and stopped MTX after 4 months. He was maintained on prednisone with normalisation of inflammatory markers and minimal fibrotic residue with low metabolic activity at follow-up.

Fourteen patients had MTX treatment suspended when in remission.

Thirteen out of 14 patients showed stable response during MTX therapy. One patient (no. 8, Table I) experienced progression of hydronephrosis, high CRP and increased metabolic activity on month 28 of MTX treatment. MTX was then discontinued, steroid dosage increased and azathioprine prescribed. Nevertheless, after 17 months, when in RPF stable response, azathioprine was discontinued due to the diagnosis of early lung cancer (she was an active smoker), made possible by the follow-up PET-MR scheduled for RPF. The patient underwent uncomplicated lobectomy with no evidence of cancer relapse at follow-up. After 18 months from lobectomy, she is still in clinical remission from RPF with low dose steroids and normalisation of CRP.

Among 13 patients in remission at the time of MTX suspension, no recurrence of RPF was observed in 12 cases (92%). One patient (no. 2, Table I) who received MTX for 30 months with stable response, showed an elevation of ESR and CRP with recurrent progression of metabolic activity of the periaortic fibrotic tissue at PET/MR 58 months after MTX interruption. She was then treated with oral prednisone, 25 mg/d, with normalisation of inflammatory markers by week 3. The reintroduction of oral MTX, 12.5 mg/weekly, made possible the progressive tapering down of prednisone to 5 mg/d over 10 weeks, together with the maintenance

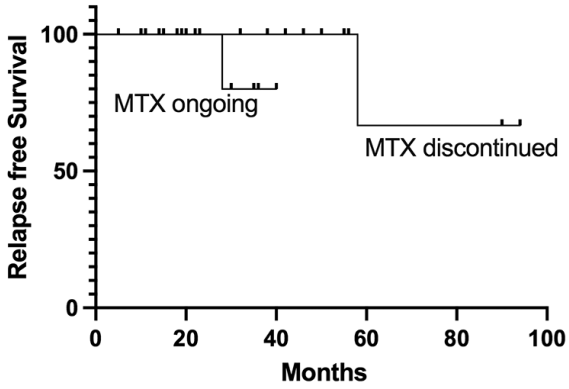


**Fig. 1.** Kaplan-Meier estimate of relapse-free survival in the 15 patients treated with MTX. "MTX ongoing" refers to relapse during MTX treatment; "MTX discontinued" refers to relapse beyond time of treatment.

of normal inflammatory values (at the 4-month follow-up).

One patient (no. 5) with stable RPF remission and negative follow-up PET-MR, was diagnosed with lung cancer 20 months after MTX discontinuation. He was a former smoker and died of metastatic disease 14 months later. Relapse-free survival is shown in Figure 1.

Liver toxicity grade 2 was documented in 2 patients and resolved with temporary dosage reduction. One patient stopped MTX autonomously due to nausea. No severe infections were recorded. All MTX-responders who required ureteral stenting at diagnosis (6/14) had it removed during the course of the follow-up.

All 4 patients refractory to first line steroid therapy who showed response to MTX were also kept on steroid during MTX. Two of them (no. 3 and 10, Table I) had steroid suspended after 9 and 12 months of MTX therapy, whereas 2 patients had a cumulative steroid dose reduction >50% compared to first line therapy. All 7 patients who relapsed after or during first line steroid therapy received a lower steroid cumulative dose during MTX treatment (3340, range 1310–6030 mg *vs*. 938, range 420–1575 mg, first line therapy *vs*. MTX). None of the patients was maintained on steroids after MTX suspension.

## Discussion

Evidences on the efficacy of alternative immunosuppression in RPF are scanty and they basically derive from treatment of other immune-mediated diseases. With regard to MTX, the first evidence of durable MTX efficacy in RPF comes from a case report published by Scavalli *et al*. (9). The association of prednisone with methotrexate was effective in one prospective study performed in 16 patients with relapsing disease (10). In this study, 11 out of 16 patients achieved remission at one year, with a median follow-up of 24 months; 4 responders who discontinued treatment relapsed shortly afterwards, whereas 7 patients who continued treatment remained in remission. Sepsis and liver toxicity was the reason for discontinuation in one patient, with temporarily interruption and dose reduction in two other patients.

Alternative immunosuppressive therapy has been proposed in RPF. The use of azathioprine or cyclophosphamide, the association of steroids and mycophenolate, and more recently the administration of rituximab in relapsing or refractory RPF or in patients with contraindications to steroids have been all shown to be effective in inducing remission in a considerable proportion of patients (11-16).

In selected patients with RPF, weekly administration of low-dose MTX as first choice immunosuppresant regimen can be appealing and well tolerated. In our experience, second line therapy with MTX was highly effective with a low rate of relapse (14.3%) following MTX interruption, compared to previously published data. This different outcome could be explained by the extended time of MTX treatment in our patients compared to the 12-month period reported in the study published by Alberici *et al*. Of note, prolonged treatment was no associated to significant toxicity although it must be underlined that one patient, a long-time smoker, was diagnosed with an early lung cancer during MTX treatment. With the exception of increased risk for skin cancer, the use of MTX was not associated with risk for other cancer in a large cohort study of patients on low dose MTX with a median follow-up of 23 months and median dosage 15 mg/wk (17). Our study was retrospective and had a small sample size. Another limitation relates to the lack of biopsy in all patients who relapsed, which does not allow to rule out IgG4-related disease. This is not unexpected as biopsies are not routinely performed in RPF due to high procedural risk (8).

In conclusion, low-dose methotrexate in combination with prednisone seems to offer an effective option for relapsing RPF, with high rate of stable remission and a relatively low risk of relapse at suspension.

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