Methotrexate plus prednisone in patients with relapsing idiopathic retroperitoneal fibrosis

Idiopathic retroperitoneal fibrosis (IRF) is a rare disease, characterised by a fibroinflammatory tissue surrounding the aortoiliac axis and frequently entrapping the ureters.[1 2] Glucocorticoids effectively induce remission, but 24% to 72% of patients relapse, half of them repeatedly.[3 4] Immunosuppressants and glucocorticoids are usually required in relapsing IRF but no studies are available.

In this prospective, open-label trial we enrolled 16 relapsing patients with IRF (July 2004 to April 2011) aged 18–85 years and with an estimated glomerular filtration rate (eGFR)>50 ml/min[5] after ureteral decompression (if required), and treated them with methotrexate and prednisone for 12 months. Relapse was defined in case of mass enlargement, hydronephrosis, or disease-related symptoms associated with high inflammatory markers.[3] Prednisone was given at 0.5–1 mg/kg/day depending on flare severity, tapered to 12.5–10 mg/day by month 3, 7.5–5 mg/day by month 6 and maintained at 5–2.5 mg/day until month 12. Methotrexate was given at 15–20 mg/week until month 12. After month 12, the clinician was free to continue or withdraw the treatment.

The primary endpoint was remission (at month 12) defined as a stable, reduced mass and absence of hydronephrosis, disease-related symptoms and normal inflammatory markers.[3] Secondary endpoints were changes in erythrocyte sedimentation rate (ESR), C reactive protein (CRP), IRF thickness and eGFR at 6–12 months and last follow-up. Patients who relapsed or stopped treatment for toxicity were considered treatment failures.

Differences in eGFR, ESR, CRP and IRF thickness were assessed using the Wilcoxon test, and relapse-free survival by the Kaplan–Meier method with comparisons between patient subgroups analysed via the log-rank test. The trial is registered with Australia New Zealand Clinical Trials Registry (ACTRN12612000845831) and was approved by the local ethics committee.

Of the 16 enrolled patients, 10 (63%) were men; the median age was 60 years. Seven patients received an initial prednisone dose of 0.8–1 mg/kg/day while nine received 0.5–0.7 mg/kg/day; the median highest methotrexate dose was 15 mg/week (IQR 14.5–17.5); the median follow-up was 24 months. Six (37%) patients had hydronephrosis and two acute renal failure.

During the first year, one patient was lost to follow-up (month 4) and one autonomously stopped treatment (month 6). The remaining 14 were assessable for response at month 12; 11 (79%) were in remission and 3 had treatment failures (due to toxicity in 1 patient and relapse in 2); the median prednisone dose at month 12 was 5 mg/day. Relapse-free survival is shown in figure 1.

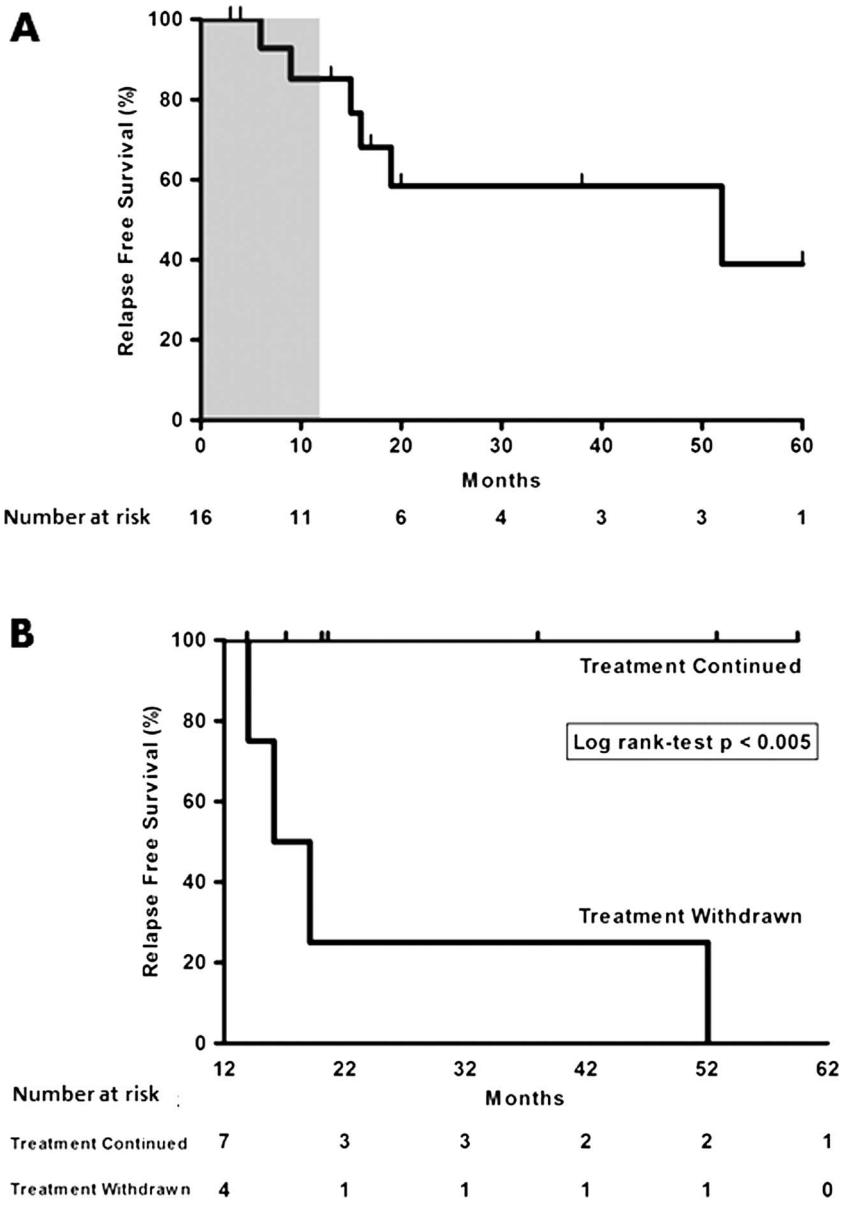

Figure 1 (A) Kaplan–Meier estimate of relapse-free survival in the 16 enrolled patients with relapsing idiopathic retroperitoneal fibrosis. The grey area indicates the planned treatment period (12 months). (B) Kaplan–Meier estimate of relapse-free survival beyond the planned year of treatment in the 11 patients who were in remission at month 12. Four of these patients discontinued treatment ('treatment withdrawn' line) whereas seven continued it ('treatment continued' line). The relapse-free survival was significantly longer in the group that continued treatment (log rank $p<0.005$).

Renal function normalised in the two patients with acute renal failure (one of them required unilateral ureteral stenting). At entry, six patients had hydronephrosis and three had a stent; at month 12, only one had hydronephrosis and two had a stent. At month 12, the median eGFR was 82 ml/min (IQR 65.8–91.5) (vs 62.8 at baseline ($p=0.234$)). ESR and CRP significantly decreased, whereas IRF thickness showed only a slight reduction (figure 2).

Among 11 patients in remission at month 12, 4 stopped treatment relapsing soon afterwards, whereas the 7 patients who continued treatment remained in remission, showing a longer relapse-free survival ($p<0.005$) (figure 1).

During the study one patient discontinued treatment for toxicity (sepsis and liver toxicity); one temporarily stopped methotrexate for enterocolitis and one reduced it for fatigue.

Our results show that methotrexate plus prednisone is a feasible option for relapsing IRF. Although different immunosuppressive agents have been successfully used for IRF,[6–9] none of them has been systematically studied in relapsing patients; biological agents may have a role but larger studies are required.[10] Our regimen induced remission in a considerable proportion of patients; acute-phase reactants normalised and renal outcome was excellent. Treatment-related toxicity was limited. After treatment withdrawal, patients may be at high risk of relapse and should be closely followed-up.

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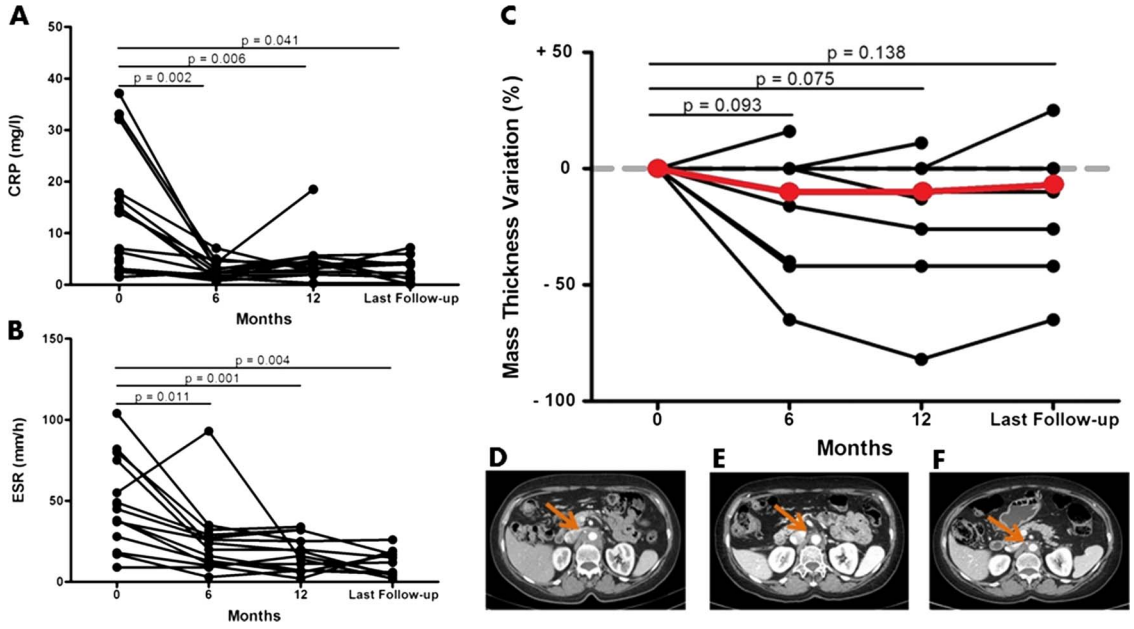

Figure 2 Secondary endpoints of our study in the 16 enrolled patients assessed at different timepoints (at study entry, after 6 and 12 months of treatment and at the end of the follow-up). (A) Variations in C reactive protein (CRP) and (B) erythrocyte sedimentation rate (ESR). After 6 and 12 months of treatment there was a statistically significant reduction in CRP level ($p=0.002$ and $p=0.006$) and ESR ($p=0.011$ and $p=0.001$). At the last follow-up, CRP and ESR were still significantly lower ($p=0.041$ and $p=0.004$) than at baseline. (C) Variations in retroperitoneal mean mass thickness. The variation is reported as percentage change compared to baseline; the red line indicates the mean variation, whereas the dashed grey line indicates baseline. A slight, non-statistically significant reduction in the mean mass thickness was observed in the whole population at months 6, 12 and at the end of the follow-up ($p=0.093$, $p=0.075$ and $p=0.138$, respectively). (D–F) Evolution of the retroperitoneal mass (arrows) assessed by contrast-enhanced abdominal CT in one of the enrolled patients, with scans taken respectively at baseline and at months 6 and 12.

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REFERENCES

1. **Vaglio A,** Salvarani C, Buzio C. Retroperitoneal fibrosis. *Lancet* 2006;**367**:241–51.
2. **Palmisano A,** Vaglio A. Chronic periaortitis: a fibro-inflammatory disorder. *Best Pract Res Clin Rheumatol* 2009;**23**:339–53.
3. **Vaglio A,** Palmisano A, Alberici F, *et al*. Prednisone versus tamoxifen in patients with idiopathic retroperitoneal fibrosis: an open-label randomised controlled trial. *Lancet* 2011;**378**:338–46.
4. **van Bommel EF,** Siemes C, Hak LE, *et al*. Long-term renal and patient outcome in idiopathic retroperitoneal fibrosis treated with prednisone. *Am J Kidney Dis* 2007;**49**:615–25.
5. **Levey AS,** Stevens LA, Schmid CH, *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–12.
6. **Scheel PJ Jr,** Feeley N, Sozio SM. Combined prednisone and mycophenolate mofetil treatment for retroperitoneal fibrosis: a case series. *Ann Intern Med* 2011;**154**:31–6.
7. **Swartz RD,** Lake AM, Roberts WW, *et al*. Idiopathic retroperitoneal fibrosis: a role for mycophenolate mofetil. *Clin Nephrol* 2008;**69**:260–8.
8. **Binder M,** Uhl M, Wiech T, *et al*. Cyclophosphamide is a highly effective and safe induction therapy in chronic periaortitis: a long-term follow-up of 35 patients with chronic periaortitis. *Ann Rheum Dis* 2012;**71**:311–12.
9. **Moroni G,** Gallelli B, Banfi G, *et al*. Long-term outcome of idiopathic retroperitoneal fibrosis treated with surgical and/or medical approaches. *Nephrol Dial Transplant* 2006;**21**:2485–90.
10. **Maritati F,** Corradi D, Versari A, *et al*. Rituximab therapy for chronic periaortitis. *Ann Rheum Dis* 2012;**71**:1262–4.

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