Positive Effect of Low-dose Imatinib Mesylate in a Patient with Nephrogenic Systemic Fibrosis

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Nephrogenic systemic fibrosis (NSF) is an iatrogenic connective tissue disorder that, until now, has only been described in patients with renal disease. Gadolinium-based contrast agent (GBCA) is associated with the development of NSF (1–3). The severity of NSF varies from mild symptoms with discrete involvement of the skin, to major involvement of the skin and reduced joint movements due to fibrosis of underlying connective tissues. Fibrosis of the inner organs and increased mortality have been described (4, 5). Different treatments have been tried, including photopheresis, topical and oral steroids, thalidomide, plasmapheresis, and intravenous sodium thiosulphate (6), but none has shown convincing effect. A case report by Panesar et al. (7) indicates a beneficial effect following kidney transplantation, while Leung et al. (8) did not find the same positive effect. Treatment with imatinib mesylate in patients with NSF has shown promising results, with reduced level of fibrosis and thus improvement in skin changes and joint contractures (9).

Imatinib mesylate is a tyrosine kinase inhibitor used primarily in the treatment of haematological malignancies. Imatinib mesylate is an inhibitor of Abelson kinase (c-Abl) and platelet-derived growth factor (PDGF) (10). c-Ab1 kinase is a direct target of transforming growth factor β1 (TGF-β1) signalling, which stimulates the fibrocytes and thus leads to tissue fibrosis (11). TGF-β1 messenger RNA has been found to be increased in skin, fascia, and striated muscle affected by NSF (12).

We describe here a severely affected NSF patient who was treated with 100 mg/day of imatinib mesylate over a period of 19 weeks with a positive effect on skin thickening and improvement in the reduced joint movements.

CASE REPORT

A 44-year-old man who had had type I diabetes since childhood, resulting in diabetic nephropathy and haemodialysis since 1985, was exposed to GBCAs five times over a period of 7 years (2001 to 2008). In 2002, the patient presented with symptoms of scleroderma, but this diagnosis was not established, as positive autoantibodies were absent and because the histopathology and clinical appearance were not characteristic for scleroderma. Differential diagnoses were excluded, and he was eventually diagnosed with an atypical scleroderma. In 2009 he was re-evaluated and diagnosed with NSF. The modified Rodnan skin score (mRss) was 17. Six months later he had progression of NSF symptoms with new inflammatory lesions of the skin. Treatment with prednisolone (20 mg/day) was initiated with a gradual reduction of 2.5 mg/every 14th day. The patient remained on a daily dose of 2.5 mg. The patient could hardly walk at this stage. Treatment with imatinib mesylate (100 mg/day) was initiated 11 days later. The walking distance improved significantly, and he was able to use his exercise bicycle again. Within the 19 weeks of treatment with imatinib mesylate, he experienced an improvement in joint contractures of both knees and the right wrist (Table I). These joints improved from 30 degrees flexion defect to normal flexion. The toes on both feet could not move, but movement was regained during the treatment. The patient was clinically evaluated 10 weeks after cessation of imatinib mesylate treatment. The improvement in his knees, wrist and toes was maintained, but the reduced movements of the hands returned. Skin thickening and tethering improved during the 19 weeks of treatment; mRss declined by 43% (from 21 to 12). At the follow-up 10 weeks later mRss was 14. Initially, the patient tolerated the treatment with imatinib well, but after 17 weeks of treatment, episodes of vomiting and nausea occurred together with an increasing C-reactive protein level. Imatinib mesylate treatment was suspended, resulting in decreased occurrence of vomiting and nausea. When imatinib mesylate treatment was reintroduced the symptoms returned, and imatinib mesylate treatment was finally discontinued.

DISCUSSION

We observed a significant improvement in an NSF patient after a short period of treatment with imatinib mesylate. The sclerodermic changes to the skin and joints decreased markedly. We speculate that the combination of imatinib mesylate and prednisolone may have had a

Table I. *Degree of joint contractures and modified Rodnan skin score (mRss) at 0 and 19 weeks of treatment with imatinib mesylate. Follow-up 10 weeks after treatment ended*

	Start of treatment (week 0)	End of treatment (week 19)	Follow-up (week 29)
Toes	No movement	Some movement	5º flexion defect, Normal extension
Right knee	30º flexion defect	Normal flexion	Normal flexion
	20º extension defect	10º extension defect	15º extension defect
Left knee	30º flexion defect	Normal flexion	Normal flexion
	15º extension defect	10º extension defect	15º extension defect
Right wrist	30º flexion defect	Normal flexion	Normal flexion
Left wrist	Normal flexion	Normal flexion	Normal flexion
Finger-pulpa distance, cm			
Right	3	0	3
Left	0	0	3
mRss	21	12	14

beneficial effect on the fibrosis. Prednisolone itself is an efficient anti-inflammatory agent, but not an antifibrotic agent. Therefore, the major role in the reduction of the fibrosis must be related to imatinib mesylate, even though it was administered in a low dosage.

In a previous study, two NSF patients were treated with 400–600 mg/dag of imatinib mesylate (9), resulting in a substantial reduction in mRss in both patients. In the first patient mRss declined by 61.9% (from 42 to 16), and in the second patient mRss declined by 83.3% (from 12 to 2), supporting the findings in our case. In systemic sclerosis (SSc), a connective tissue disease of unknown aetiology with progressive fibrosis of the skin and a variety of internal organs, a positive effect on the fibrosis is usually observed within 6–12 months after treatment with conventional therapy. Van Daele et al. (13) treated a patient with refractory SSc with 400 mg/day of imatinib mesylate and observed a 33.3% decline in mRss (from 18 to 12). Sfikakis et al. (14) made a similar observation in a patient with refractory SSc, who was also treated with 400 mg/day of imatinib mesylate; they observed a 36.4% decline in mRss (from 44 to 28). In parallel, Kay & High (9) observed that NSF symptoms returned rapidly after discontinuation of imatinib mesylate treatment, but improved after reinstatement. Our observations suggest that imatinib mesylate in smaller doses may have a beneficial effect on fibrosis in NSF and could be beneficial for some NSF patients who are unable to tolerate a larger dosage of imatinib mesylate.

The authors declare no conflicts of interest.

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