Lymphoedema associated with sirolimus treatment

Lucy Martin

Abstract

Background: Secondary lymphoedema is a chronic condition that has a financial, emotional and physical impact and causes a decrease in quality of life for affected patients. Twenty cases of lymphoedema presenting in patients undergoing sirolimus immunosuppresive therapy, for renal or hepatic transplantation, have been reported since 2004. Although some patients showed a marked improvement after cessation of sirolimus treatment, more recent reports have emerged of patients who show little or no improvement and must learn to adapt to manage this chronic condition. ***Aims:*** This review aims to summarise the cases that have been reported so far and identify areas of future study that may lead to improved methods of avoiding or managing this complication of sirolimus therapy. ***Methods:*** A literature review was carried out focusing on chemically induced lymphoedema using the National Library of Medicine's Medline database. ***Results:*** A Medline search revealed 20 cases of sirolimus-induced lymphoedema to date, 18 in kidney transplant patients. There has also been a reported case of lymphoedema as a side effect in a paediatric renal transplant patient treated with sirolimus. ***Conclusions:*** The fact that there is an increasing number of reports of transplant patients developing lymphoedema after having sirolimus therapy demonstrates that this area requires further investigation. ***Declaration of interest:*** None.

Key words

Lymphoedema
Sirolimus
Renal/hepatic transplantation
Immunosuppression

Lymphoedema is a debilitating condition that can be of either primary or secondary (acquired) cause. It is the result of an accumulation of protein-rich fluid due to a failure of lymphatic drainage, often due to an obstruction (Rockson, 2001). Lymphoedema usually affects one or more limbs, but can also occur in other organs (Szuba and Rockson, 1998). When the condition is chronic, lymphoedema can have a financial, emotional and physical impact on patients, which can decrease their quality of life (Rockson, 2001; Maguire, 2004).

Lucy Martin, BTech (forensic chemistry), BSc (hons), is a medical student at the Lymphoedema Research Unit, Department of Surgery, at the School of Medicine, Flinders University in Adelaide, South Australia

Long-term management can require:

- Elevation
- Manual lymph drainage
- The use of compression garments
- Low-level laser therapy
- The need for meticulous skin care
- In some instances, surgery (Moseley and Piller, 2002).

Secondary lymphoedema is estimated to develop in up to 30% of people who undergo cancer surgery and/or radiotherapy, but can also be due to any other surgery that disrupts lymphatic flow, particularly in the limbs and abdomen (Moseley and Piller, 2002). Trauma, infection and idiopathic causes of lymphoedema have also been identified (Rockson, 2001).

One of the causes of secondary lymphoedema is the use of sirolimus in transplant patients (Aboujaoude et al, 2004; Romagnoli et al, 2005; Al-Otaibi et al, 2007; van Onna et al, 2007; De Bartolomeis et al, 2008; Desai et al, 2009; Damasiewicz and Ierino, 2010). Siroliomus is an inhibitor of the mammalian target of rapamycin (mTOR), used as an immunosuppressive agent in renal and hepatic transplants — mTOR is involved in protein synthesis pathways that lead to cell growth and proliferation, as well as the proliferation of B and T cells (Mehrabi et al, 2006). It was introduced in 2000 in the US as a combined therapy to be used with cyclosporine A and tacrolimus (other immunosupressive agents), as these combinations were found to cause a decrease in acute rejection episodes (Katz et al, 2000).

Sirolimus does not have some of the common side effects of other immunosuppressive agents, including:

- Nephrotoxicity
- Neurotoxicity
- Diabetes mellitus
- Hypertension.

Some of the side effects of sirolimus include:

- Hyperlipidaemia
- Lung problems including pneumonia

- Proteinuria
- Pancytopenia
- Lymphocele formation
- Diarrhoea
- Fatigue
- Nausea (Mehrabi et al, 2006).

Sirolimus has also been reported as inducing eyelid oedema and angioedema (Mohaupt et al, 2001; Wadei et al, 2004; Mahe et al, 2007). As mentioned, lymphoedema has also been reported as a complication of sirolimus (Aboujaoude et al, 2004) and it does not always improve after cessation of the drug (Desai et al, 2009).

Results

A Medline search revealed 20 cases of sirolimus-induced lymphoedema to date, 18 in kidney transplant patients (Aboujaoude et al, 2004; Romagnoli et al, 2005; Al-Otaibi et al, 2007; De Bartolomeis et al, 2008; Desai et al, 2009; Damasiewicz and Ierino, 2010) and two in liver transplant patients (van Onna et al, 2007; Desai et al, 2009). There has also been a reported case of lymphoedema as a side effect in a paediatric renal transplant patient treated with sirolimus by Ibanez et al (2005).

There was variability in many features of these cases. The distribution of the patient ages in the cases reported is shown in *Figure 1*, with the mean patient age found to be 46. Eleven patients were female and nine male, which is expected, as there is no reason why this type of secondary lymphoedema should affect one sex more than the other. All cases occurred after sirolimus was started, although some patients presented as soon as 11 weeks after commencement, whereas other cases involved patients who had been on a more stable regimen (*Figure 2*). Two cases involved patients who were stable on sirolimus for two and a half years before onset, while one case involved a patient who had been stable on sirolimus therapy for three years. A weak negative correlation was found between age and lymphoedema onset. However, this became slightly stronger when the 59-year-old women who experienced lymphoedema after 30 months on sirolimus treatment was excluded from analysis as she had a trauma to the area, in the form of an insect bite, which was a potentially confounding factor (Damasiewicz and Ierino, 2010).

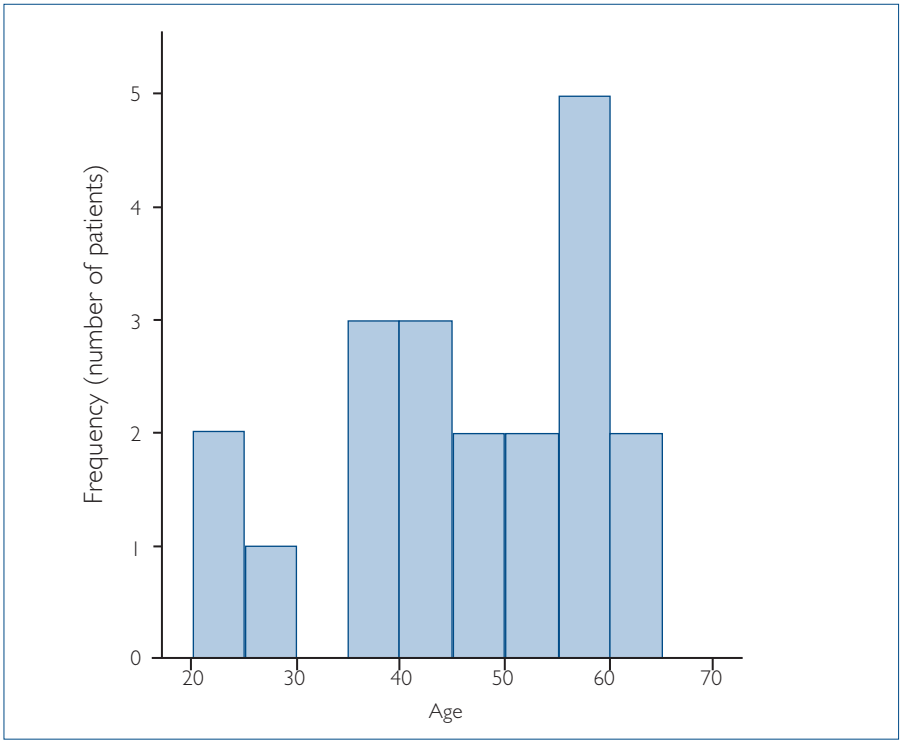

Figure 1. Age distribution of reported cases of patients with sirolimus-associated lymphoedema.

There was also variability in the area affected, with bilateral lower limbs affected often, although one usually more severely than the other. Upper extremities were also commonly affected, as well as breasts, flanks and genitals. Ascites were present in one patient.

'When the condition is chronic, lymphoedema can have a financial, emotional and physical impact on patients, which can decrease their quality of life'

Doses were all within the therapeutic range and there was a mixture of resolved symptoms, improved symptoms and no improvement after cessation of the treatment (*Figure 3*). Kruskal-Wallis testing showed no association between sirolimus dose and outcome (p=0.143), no association between duration of sirolimus therapy and outcome (p=0.454) and no association between lymphoedema onset and outcome (p=0.309).

All lymphoedema was investigated thoroughly for other possible causes. There was no history of familial lymphoedema or malignancy in any patient and only one patient had a previous trauma to the affected area, that, although likely to explain the initial symptoms, did not explain the persistent long-term lymphoedema (Damasiewicz and Ierino, 2010). Lymphoscintigraphy was undertaken in some cases and showed either lymphatic obstruction (Romagnoli et al, 2005; Al-Otaibi et al, 2007), delayed lymphatic drainage, or failure of either the initial lymphatics or superficial collectors (Desai et al, 2009), although one case showed no obstruction or delay (De Bartolomeis et al, 2008). Arteriovenous fistulas were present in some patients with upper limb involvement on the same side, although lower limbs were involved as well (Aboujaoude et al, 2004, Romagnoli et al, 2005, Desai et al, 2009). There was no correlation between the side most affected by the lymphoedema and the site of the hepatic or renal transplantation.

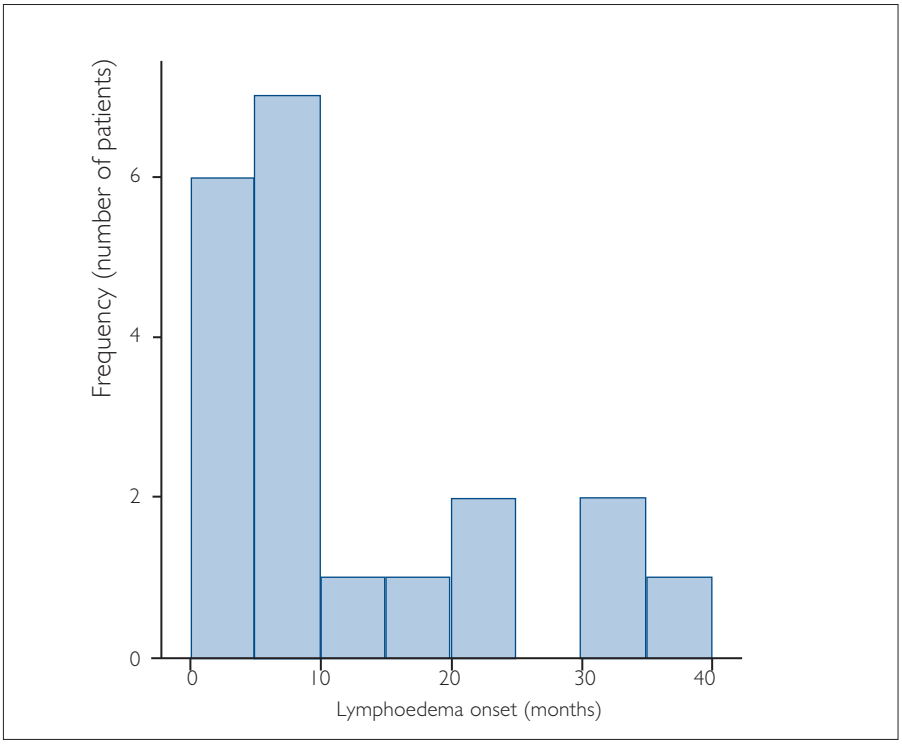

Figure 2. Months on sirolimus therapy before lymphoedema onset in the reported cases.

Discussion

The reported number of cases of sirolimus causing lymphoedema is low. Aboukaoude et al (2004) reported that of 138 renal and renal-pancreatic transplants performed over five years in their institution, only three cases of lymphoedema were observed. Despite this, it is of concern that, in the recent cases reported by Desai et al (2009), only one out of eight showed significant improvement after therapy was stopped. Other case studies showed patients who had undergone only mild and moderate improvement (Romagnoli et al, 2005; Al-Otaibi et al, 2007).

Overall, 35% of the 20 cases reported experienced no improvement after cessation of sirolimus therapy and 10% only mild improvement, meaning almost half of the patients suffered permanent lymphoedema from the treatment with a further 15% only exhibiting moderate improvement. There may be further cases reported if sirolimus continues to be used either along with cyclosporine A and/or tacrolimus instead of these agents, due to its decreased nephrotoxicity. This will allow further analysis of any trends, particularly relating to outcomes. The incidence of lymphoedema after sirolimus treatment may also be underreported. The reports of lymphoedema following sirolimus treatment have mainly been the focus of case studies at this time and, therefore, no formal statistical analysis evaluating incidence/prevalence has been completed.

There is a suggestion that by identifying patients early and stopping sirolimus treatment there may be a decreased chance of lymphoedema (Damasiewicz and Ierino, 2010), however, the recent reports of persistent symptoms seem to contradict this. More formal analysis is required in a larger range of patients to determine any such trends. It is, however, important to identify patients that are affected and rule out other causes so that targeted management can begin as early as possible (Maguire, 2004). The early identification of sirolimus as a possible cause of secondary lymphoedema may also prevent the patient from undergoing a barrage of invasive and expensive investigations to rule out other causes (Szuba and Rockson, 1998).

Information about how sirolimus causes lymphoedema may also be vital, firstly in identifying patients at increased risk of lymphatic obstruction and then ceasing or avoiding sirolimus treatment. It may also potentially provide further information on the drainage of the lymphatic system. Three mechanisms have been proposed so far but no further work has been done to establish the validity of these hypotheses (Aboujaoude et al, 2004; Romagnoli et al, 2005; Desai et al, 2009).

Aboukaoude et al (2004) proposed that the lymphoedema was secondary to the multiple vascular procedures these transplant patients underwent, leading to disrupted integrity of the lymphatic system and increased lymphatic load. The fact that there was involvement of limbs that were not affected by the surgery is not fully explained by this hypothesis. Romagnoli et al (2005), hypothesised that the lymphoedema may be due to engorged lymphatic vessels as a result of sirolimus. These vessels may then be compressed by other structures leading to eventual obstruction of the lymphatic system. Romagnoli et al agreed with Aboukaoude et al, however, especially as the cases they reported had patients with arteriovenous fistulas on the same side as the lymphatic obstruction, supporting the theory of enhanced lymphatic flow and disruption of the vessels. The cause of the lymphoedema may, therefore, be of multifactorial origin, being related to both the sirolimus treatment as well as the loss of integrity of the lymphatic system due to multiple vascular procedures.

Desai el al (2009) have more recently proposed that sirolimus acts to inhibit the actions of the vascular endothelial growth factors (VEGF) C and D, which are responsible for lymphatic proliferation. This theory is supported by the fact that the mTOR receptor is part of the downstream signalling pathway of the VEGF receptor, and *in vitro* studies have shown that sirolimus is capable of inhibiting lymphangiogenesis (Huber et al, 2007; Kobayashi et al, 2007).

Potentially, all three suggested that various mechanisms are involved, as the low incidence of sirolimus-induced lymphoedema makes it likely to be of multifactorial origin. Therefore, decreased lymphangiogenesis, surgically disrupted vessels, engorged lymphatic vessels and increased lymphatic load may all occur in

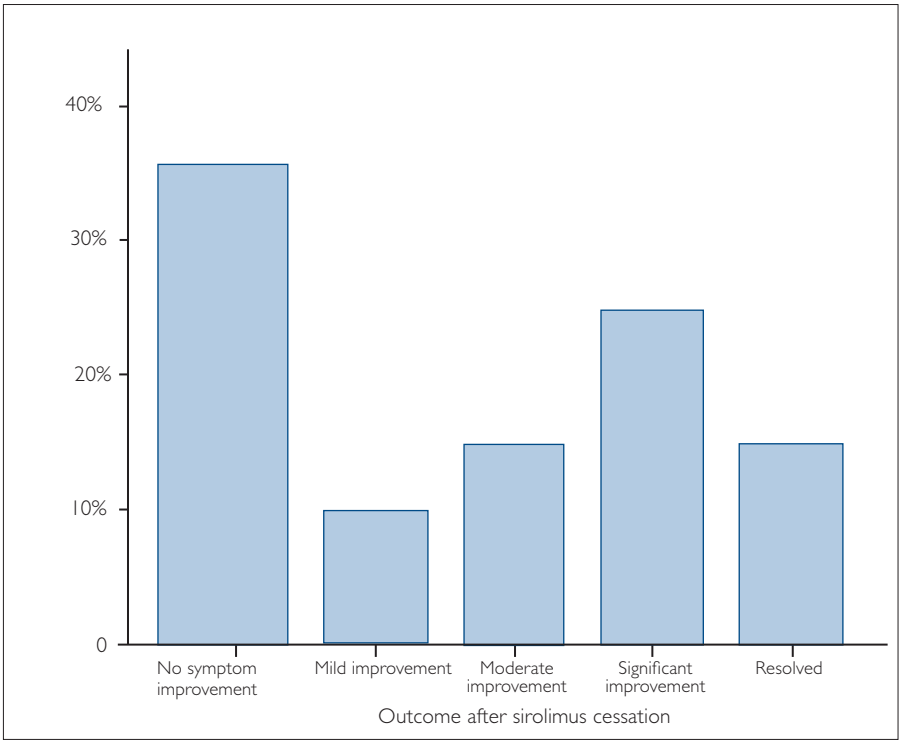

Figure 3. Outcomes after cessation of sirolimus treatment for the reported cases.

Key points

- Lymphoedema has been shown to develop after sirolimus use in transplant patients.
- A Medline search revealed 20 cases of sirolimus-induced lymphoedema to date.
- There has been suggestion that by identifying patients early and stopping sirolimus treatment, there may be a decreased chance of lympoedema.
- Early identification of sirolimus as a cause of secondary lymphoedema may prevent invasive and expensive investigations to rule out other causes.

those patients affected by lymphoedema following sirolimus treatment. Therefore, further studies aimed at identifying the effects of sirolimus on the lymphatic system with greater certainty are required.

Conclusion

The increasing number of reports of transplant patients developing lymphoedema after undertaking sirolimus therapy indicate that this is an area that requires further investigation. Specific focus on the differences in patients whose symptoms are resolved after cessation and those who continue to experience lymphoedema may be important. Determining the mechanism is also important and could potentially play a role in reducing the incidence by identifying at-risk patients and uncovering strategies to help with the management of lymphoedema caused by sirolimus treatment. JL

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