Clin Kidney J (2014) 7: 115–120
doi: 10.1093/ckj/sfu001
Advance Access publication 24 February 2014

Minireview

CKJ

Oedema, solid organ transplantation and mammalian target of rapamycin inhibitor/proliferation signal inhibitors (mTOR-I/PSIs)

Chems Gharbi, Victor Gueutin and Hassan Izzedine

Department of Nephrology, Pitié Salpetriere Hospital, Paris, France

Correspondence and offprint requests to: Hassan Izzedine; E-mail: hassan.izzedine@psl.aphp.fr

Abstract
Mammalian target of rapamycin inhibitor (mTOR-I)/proliferation signal inhibitors (PSI) including sirolimus and everolimus represent a new class of drugs increasingly used in solid-organ transplantation as alternatives to calcineurin inhibitors for patients with renal dysfunction, transplant coronary arterial vasculopathy or malignancy. The most frequently occurring mTOR-I/PSI-related adverse events are similar to those associated with other immunosuppressive therapies, but some side effects are more characteristic of proliferation signal inhibitors (e.g. lymphocele, arthralgia, oedema and hyperlipidaemia). The present paper review incidence, clinical presentation and mechanism of oedema within the clinical experience of mTOR-I/PSI in solid organ transplantation.

Keywords: angio-oedema; oedema; everolimus; lymphoedema; proliferation signal inhibitor; sirolimus; VEGF-C

Mammalian target of rapamycin inhibitor (mTOR-I)/proliferation signal inhibitors (PSI) including sirolimus (SRL) and everolimus (EVL) represent a new class of drugs increasingly used in solid organ transplantation as alternatives to calcineurin inhibitors for patients with renal dysfunction, transplant coronary arterial vasculopathy (TCAV) or malignancy [1]. Though generally well tolerated, the use of mTOR-I/PSI is associated with many side effects, which may account for the 20–40% drop-out rate for SRL/EVL in clinical Phase III trials. Some side effects are easily manageable, whereas others lead to drug discontinuation [2]. Oedema induced by mTOR-1/PSI takes different clinical forms ranging from the banal lymphocele to the dramatic angio-oedema (AE). This article reviews the incidence (Table 1) [3–13], clinical presentation (Table 2) [14–24] and mechanisms of oedema within the clinical experience of mTOR-I/PSI in solid organ transplantation.

Lymphocele

Lymphocele is a well-known complication after kidney transplantation. It occurs among 0.6–22% of symptomatic patients being treated with cyclosporine (CsA)-based immunosuppression [25–31] and 49% of asymptomatic cases detected by ultrasonography during a 2- to 11-year follow-up [32]. mTOR-I/PSI are associated with an increased incidence of mild or moderate lymphocele. In clinical studies, the rates of lymphocele in renal transplant patients receiving a 6-month treatment with EVL 1.5–3.0 mg/day, or SRL 2.0–5.0 mg/day were 6.4–15.2 [33] and 12–13% [34], respectively. Post-marketing experience with SRL has demonstrated an increased incidence of lymphoceles. Factors predisposing to lymphocele formation include drainage from open lymphatics divided during surgery to dissect the host iliac vessels [29, 35], injured lymph channels in the donor kidney hilum vessels [31, 36], acute allograft rejection episode [26, 37, 38], acute tubular necrosis [26], transplant kidney biopsy [30], retransplantation [39] and adult polycystic kidney disease as the original renal disease [40]. Clinical experience shows that mild lymphocele can resolve itself, while moderate lymphocele usually responds to povidine-iodine [41]. Although some patients who receive mTOR-1/PSI may develop early massive lymphocele that requires surgery, mTOR-1/PSI dose reduction or complete withdrawal is not necessary. Surgery for lymphocele is not common [42].

Eyelid oedema

Eyelid swelling is often the herald of significant systemic or periorbital disease. The aetiological list is extensive. Many medications—topical, oral and parenteral—are well recognized to create eyelid swelling through generalized fluid retention, AE, urticaria or topical blepharoconjunctivitis. mTOR-1/PSI-related eyelid oedema in kidney transplant recipients was described in a few case reports of SRL- [18, 23] and EVL-based [43] treatments. Development of eyelid oedema was gradual, occurring over 1–5 months after starting mTOR-I/PSI. The oedema may be mild and easily managed with low-dose furosemide and reduction of SRL dose was not warranted. In some patients, discontinuation of mTOR-I/PSI was followed by delayed resolution of the swelling, with full recovery taking as long as months. The underlying mechanism is unknown.

Table 1. Incidence of oedema induced by EVL in solid organ transplantation

Author	Study	Organ transplant	Follow-up (months)	EVL mean level and/or mean dosage	Oedema incidence	
					EVL	Control
Lehmkuhl *et al.* [3]	Multicentre open-label study RAD2411	Heart transplant	12	4.1 ± 1.8 ng/mL	EVL, 91 patients Peripheral oedema, 39.6% Pericardial effusion, 35.3% Pleural effusion, 24.2%	MMF, 83 patients Peripheral oedema, 34.9% Pericardial effusion, 25.3% Pleural effusion, 13.3%
Gullestad *et al.* [4]	Multicentre randomized trial	Heart (*n*=190) and lung (*n*=92) transplant	12	3–8 ng/mL	EVL+, 140 (29.3%)	EVL−, 142 (8.5%)
Gullestad *et al.* [5]	Multicentre randomized trial	Heart (*n*=190) and lung (*n*=92) transplant	24	4.5 ± 1.4 ng/mL	EVL+, 103 (8.3%)	EVL−, 119 (8.7%)
Roman *et al.* [6]	Retrospective, EVERODATA lung substudy	Lung transplant	12	6.4 ± 2.8 ng/mL	5/65 (7.7%	
De Simone *et al.* [7]	Randomized controlled trail, H2304 study group	Liver transplant	12	6–10 ng/mL	EVL+ reduced TAK 43/245 (17.6%)	TAC elimination, 42/231 (18.3%) TAC control, 26/243 (10.8%)
Alegre *et al.* [8]	Retrospective	Liver transplant	48	5.5 ± 2.2 ng/mL	EVL overall, 13/57 (28.8%)	EVL monotherapy, 5/24 (20.8%) EVL combination 8/30 (24.2%)
Saliba *et al.* [9]	Randomized controlled trail, H2304 study group	Liver transplant	24	AE	EVL+ reduced TAC, 6/245 (2.4%)	TAC elimination, 4/231 (1.7%) TAC control, 5/243 (2.1%)
				Ascites	EVL+ reduced TAC, 11/245 (4.5%)	TAC elimination, 14/231 (6.1%) TAC control, 11/243 (4.5%)
				Peripheral oedema	EVL+ reduced TAC, 55/245 (22.4%)	TAC elimination, 45/231 (19.7%) TAC control, 36/243 (14.9%)
				Pleural effusion	EVL+ reduced TAC, 15/245 (6.1%)	TAC elimination, 7/231 (3.1%) TAC control, 13/243 (5.4%)
Lorber *et al.* [10]	Randomized, multicentre Phase III study	Kidney transplant	36	EVL 1.5 mg/d	101/193 (52.3%)	MMF, 82/196 (41.8%)
				EVL 3 mg/d	92/191 (47.4%)	MMF, 82/196 (41.8%)
Cotovio *et al.* [11]	Retrospective register-based study	Kidney transplant	6	5.9 ± 2.6 ng/mL	8 (5.3%)	–
Shihab *et al.* [12]	Randomized controlled trial	Kidney transplant	12	<3 ng/mL	18/29 (62.1%)	–
				3–6 ng/mL	94/212 (44.3%)	–
				6–8 ng/mL	55/105 (52.4%)	–
				≥8 ng/mL	17/26 (65.4%)	–
Takahashi *et al.* [13]	Multicentre, open-label randomized study	Kidney transplant	12	1.5 mg/day	EVL, 20/61 (32.8%)	MMF, 8/61 (13.1%)

MMF, mycophenolate mofetil; TAC, tacrolimus.

Table 2. Case reports of oedema induced by mTOR-I/PSIs: clinical features

Reference	Organ transplant	mTOR-I/PSI		Oedema			
		Dosage	Level	Onset	Clinical features	Action	Follow-up
[14]	Heart	EVL, 0.75 mg/day	8 ng/mL	1 month	Hand and forearms	EVL dose reduction	Partial resolution
		EVL, 0.5 mg/day	5 ng/mL	1 month	Hand and forearms		Partial resolution
		Switch to SRL, 1 mg/day	10 ng/mL	Few days	Increase in the oedema	Stop	Complete resolution 2 months after
[15]	Heart	EVL,	NA	36 months	Bilateral chylothorax	Switch EVL to MMF	Complete resolution within 8 months
		Reintroduction of EVL (TCAV progression)	NA	4 months	Pleural effusion	EVL discontinuation	Complete resolution
[16]	Kidney	EVL, 0.5–1 mg/day	>3 ng/mL	12 months	Feet oedema	No EVL discontinuation	Progression to upper extremities and left breast Complete resolution within 3 months
[17]	Kidney	EVL, 1.5 mg/day (6 patients)	3–8 ng/mL	2–41 days	AE	Hospitalization IV prednisone and clemastin Acetyl-salicylic acid stopped	Five patients were free from recurrence despite EVL maintenance. One patient experienced two recurrent episodes before under EVL, stopped
[18]	Kidney	SRL, dosage NA	NA	3 months	Mild oedema on both legs, LUE and left breast, recurrent lymphangitis	SRL discontinuation	Complete resolution within few months
	Kidney	SRL, dosage NA	NA	6 months	Mild oedema on both legs and redness of RUE and right breast,	SRL discontinuation	Partial resolution, 60–70% within few months
	Kidney	SRL, dosage NA	NA	4 months	Oedema both legs, nephrotic syndrome	SRL discontinuation	Partial resolution, 80–90% within few weeks
[19]	Kidney	SRL, 9.5 mg/day	26.3 ng/mL	36 months	Severe oedema and redness of LUE and left breast,	Reduction of SRL dosage (trough levels of 5–10 ng/mL)	Partial resolution, 60–70%
	Kidney	SRL, 2 mg/day	5–10 ng/mL	6 months	Severe oedema of RUE and right breast, functioning access RUE	SRL withdrawal, conversion to CSA	Partial resolution, 70–80%
[20]	Kidney	SRL, 3 mg/day	10–18 ng/mL	30 months	Lymphoedema of the left upper limb	SRL withdrawal	Significant improvement
	Kidney	SRL, 3 mg/day	10–15 ng/mL	30 months	Lymphoedema of the left lower limb	SRL withdrawal	Significant improvement within few months
	Kidney	SRL, 3 mg/day	10–18 ng/mL	24 months	Lymphoedema of the left lower limb	SRL withdrawal	Significant improvement within few months
[21]	Kidney	SRL, 5 mg/day	12–20 ng/mL	3 months	Generalized lymphoedema	SRL withdrawal	Complete resolution 3 months after
[22]	Kidney	SRL, 19 mg/day	10.3 ng/mL	1 month	AE	Steroids + diphenhydramine and SRL withdrawal	Complete resolution 2 days after
	Kidney	SRL reintroduction, 20 mg/day	3.1 ng/mL	1 day	AE	Steroids + diphenhydramine and SRL withdrawal	Complete resolution 2 days after
	Kidney	SRL, 8 mg/day	19.4 ng/mL	14 days	AE	Steroids + diphenhydramine and SRL withdrawal	Complete resolution 2 days after. However, the patient inadvertently received two more daily 4 mg doses of SRL, and AE recurred. SRL was then switched to cyclosporin A, and there has been no recurrence in the subsequent 11 months
[23]	Kidney	SRL, 1–20 mg/day (5 patients)	5–19 ng/mL	1–5 months	Eyelid oedema of variable severity	Dose reduction, temporary or definitive SRL discontinuation	Complete resolution
[24]	Heart	SRL, 2 mg/day	2.5 ng/mL	12 months	Facial and right arm oedema	SRL withdrawal	Complete resolution 6 weeks after

EVL, everolimus; SRL, sirolimus; TCAV, transplant coronary arterial vasculopathy; NA, not available; LUE, left upper extremity; RUE, right upper extremity; RLE, right lower extremity; CSA, cyclosporine.

Oedema and lymphoedema

Leg swelling is an extremely frequent symptom with a broad variety of largely differing causes. The most important mechanisms behind the symptom include venous and lymphatic pathology, volume overload, increased capillary permeability and lowered oncotic pressure. Therefore, the most frequent diseases associated with leg swelling are deep vein thrombosis and chronic venous insufficiency, primary or secondary lymphoedema, cardiac failure, hypoproteinaemia, idiopathic cyclic oedema and drug-induced oedema. Lymphoedema may be primary (congenital lymphatic abnormality) or secondary, frequently related to cancer treatment. Other causes of secondary lymphoedema include obstruction by tumour, infection (filariasis), recurrent cellulitis and connective tissue disease. A less-common form of oedema is lymphoedema, which causes an abnormality in the lymphatic system. The most common cause is interruption of the axillary lymphatic system by surgery and/or radiation therapy in women with breast cancer.

Unilateral or bilateral peripheral oedema/lymphoedema is common following the initiation of mTOR-I/PSI use [24, 43] and frequently sufficiently severe enough to require medication discontinuation. However, it may be less frequent with EVL with a retrospective series reporting 4- to 5-fold less oedema when compared with matched SRL-treated patients (14 versus 64%), respectively [14]. It has been mentioned that a preponderance in any specific gender is unlikely and it develops 7 months to 2 years after the start of SRL (mean SRL levels ranging from 10 to 20 ng/mL) [20] or a few days to 36 months after the start of EVL (mean EVL levels ranging from 3 to 26 ng/mL) in an arm- or leg-localized lymphoedema form of varying severity (Table 2). Usually, peripheral oedema/lymphoedema was controlled with low doses of furosemide accompanied by reduction of the immunosuppressant [43]. mTOR-I/PSI-related lymphoedema is not dependent on its cumulative dosage and exposure duration. [20] Early discontinuation of the drug may prevent permanent disfigurement [44]. Moreover, the occurrence of limb lymphoedema in renal transplant recipients under SRL treatment, especially if on the same side as the haemodialysis access, should alert the transplant physician to the need for rapid SRL reduction or withdrawal, before complete obstruction occurs, further complicating an already disabling condition. [19] Close monitoring of this side effect is warranted. Recognizing this association may prevent many unnecessary, costly and invasive investigations. The pathophysiology seems to be due to altered lymphatic drainage [18, 19]. The lymphatic vasculature transports extravasated tissue fluid, macromolecules and cells back into the blood circulation. One pathway of regulation of cell growth and proliferation is mediated by the regulatory associated protein of mTOR (raptor)—G protein β-subunit-like protein (GβL)—and mTOR complex, which is a target of rapamycin. Important downstream effectors of the mTOR system are the translation regulators p70S6 kinase and eukaryotic initiation factor 4E-binding protein [45]. The mTOR pathway is regulated by the PI3K/AKT kinase system, which is upregulated in tumours. Activation of PI3K/AKT causes activation of mTOR and promotes cell growth and proliferation. Lymphatic endothelium expresses VEGF receptor-3 (VEGFR-3), which is activated after binding to VEGF-C, and VEGF-D plays an important role in lymphangiogenesis. The gene that encodes VEGFR-3 (FLT4) is defective in most families with congenital hereditary lymphoedema [46] and impaired lymphangiogenesis and lymphoedema is observed in soluble VEGFR-3 (VEGF-C/VEGFD signaling inhibitor) expressing transgenic mice [47]. Missense mutations of VEGFR-3 prevent normal lymphatic growth in humans [46]. Huber *et al.* [48] demonstrate that rapamycin interferes with the intracellular VEGF-C-activated pathway of lymphatic endothelial cells. In rapamycin-treated animals, the anti lymphangiogenic effect during tissue regeneration occurs with prolonged lymphoedema, emphasizing the clinical relevance of this effect of the mTOR inhibition in solid organ transplant recipients.

Effusions

An increased incidence of pleural and pericardial effusions has been described in mTOR-I/PSI-treated renal and cardiac transplant patients. The frequency of pericardial effusions following cardiac transplant is 3-fold greater in SRL-treated patients often requiring interventions such as drainage with or without SRL dose reductions [49–51]. The prevalence of effusions, pleural and pericardial, is similar between mycophenolate mofetil-(MMF) and EVL-treated patients, suggesting that this side effect may be PSI specific with greater frequency seen in SRL- versus EVL-treated patients [3]. Cases of pericardial tamponade have been described following the initiation of SRL both in *de novo* cardiac and late conversion heart transplant patients as well as non-cardiac transplants patients [50, 51].

Angio-oedema

AE is a self-limiting swelling that occurs in the deeper cutaneous and mucous membrane layers. Most cases of AE result from a reaction to food or drugs, but some episodes have no identifiable trigger.

Drug-induced AE is well documented in patients taking angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor antagonists (AIIRA), fibrinolytic agents, oestrogens and nonsteroidal anti-inflammatory drugs [52]. In addition, the frequency of ACEI-induced AE is high in transplant recipients, estimated at ∼1–5 versus 0.1–0.5% in the general population [53, 54]. Abbosh *et al.* [54] reported a 24- and 5-fold higher incidence of AE in cardiac and renal transplant recipients, respectively, who were maintained on cyclosporin A, azathioprine and prednisone when compared with the general population. Several reports focused on the putative role of mTOR-I/PSI (SRL and EVL) in the pathogenesis of AE in organ transplant recipients [17, 22, 55–58]. In previous reports, AE associated with SRL occurred in 2.2–15% of patients [57, 59]. The associated risk factors were ACEI therapy or African-American patients taking metoprolol [55, 57], which are known to be associated with a higher frequency of AE [60–62]. Fuchs *et al.* [17] reported that 6 out of their 114 patients (5.3%) experienced for the first time in their lives the occurrence of lingual AE after switching them over to EVL. The time period from starting mTOR-I/PSI to the occurrence of AE ranged from 1 to 41 days. In all six patients, the AE was associated with petechial bleeding and with lingual bullae on the lateral part of the tongue and required hospitalization. At the time when the AE occurred, the following concomitant medications were used: acetyl-salicylic acid (ASS), ACE inhibitors or angiotensin-1-receptor inhibitors. Because the symptoms ceased after

discontinuation of ASS in five out of the six patients, it may well be that ASS has triggered the occurrence of EVL-associated side effects. However, the time course after initiation of the immunosuppressive drug, the recurrence in one patient, and the favourable outcome after stopping the drug provide an argument for the pathogenic link between EVL and tongue AE [17]. Lingual oedema seems to occur predominantly within the first weeks after initiation of mTOR-I/PSI therapy. Drug trough level at presentation is variable within or below the target level or in the toxic range [17]. A lack of C1-esterase inhibitor could be excluded in all patients. A history of food and/or drug allergies and a lack of C1-esterase inhibitor could be excluded in all patients. In all cases, the condition responded promptly to parenteral steroids, H1 and H2 blockers and discontinuation of SRL. In the majority of patients, the AE seems to disappear without further recurrence after adequate therapy of the symptoms. The responsibility of mTOR-I/PSI in the pathogenesis of AE is suggested either as the sole aetiological factor or more probably as a cofactor [17, 22, 56, 57] Several hypotheses can be advanced to explain the potential triggering role of mTOR-I/PSI: cytochrome p450 3A4 metabolism pathway interaction [63–65], experimental interaction between mTOR-I/PSI and the bradykinin pathway [66] and autoimmune diseases induced by mTOR-I/PSI introduction [67]. The absence of urticaria with AE suggests that mTOR-I/PSI-associated AEs are not IgE mediated [17, 22, 56, 57].

In conclusion, mTOR-I/PSI may facilitate the occurrence of oedema. This specific adverse event can be easily managed without discontinuation of the drug. It is important to be aware of this phenomenon to avoid burdensome and cost-intense investigations for patients showing this symptom during treatment with mTOR-I/PSI.

Conflict of interest statement. None declared.

References

1. Valantine H, Zuckermann A. From clinical trials to clinical practice: an overview of Certican (everolimus) in heart transplantation. *J Heart Lung Transplant* 2005; 24(Suppl 4): S185–190
2. Rostaing L, Kamar N. mTOR inhibitor/proliferation signal inhibitors: entering or leaving the field? *J Nephrol* 2010; 23: 133
3. Lehmkuhl H, Ross H, Arizon J *et al*. Comparability of pattern of occurrence of pericardial effusions between everolimus- and MMF-based regimen in de novo cardiac transplant recipients. *J Heart Lung Transplant* 2009; 28(2 Suppl 1): S170
4. Gullestad L, Iversen M, Mortensen SA *et al*. Everolimus with reduced calcineurin inhibitor in thoracic transplant recipients with renal dysfunction: a multicenter, randomized trial. *Transplantation* 2010; 89: 864–872
5. Gullestad L, Mortensen SA, Eiskjær H *et al*. Two-year outcomes in thoracic transplant recipients after conversion to everolimus with reduced calcineurin inhibitor within a multicenter, open-label, randomized trial. *Transplantation* 2010; 90: 1581–1589
6. Roman A, Ussetti P, Zurbano F *et al*. A retrospective 12-month study of conversion to everolimus in lung transplant recipients. *Transplant Proc* 2011; 43: 2693–2698
7. De Simone P, Metselaar HJ, Fischer L *et al*. Conversion from a calcineurin inhibitor to everolimus therapy in maintenance liver transplant recipients: a prospective, randomized, multicenter trial. *Liver Transpl* 2009; 15: 1262–1269
8. Alegre C, Jiménez C, Manrique A *et al*. Everolimus monotherapy or combined therapy in liver transplantation: indications and results. *Transplant Proc* 2013; 45: 1971–1974
9. Saliba F, De Simone P, Nevens F *et al*.; H2304 Study Group. Renal function at two years in liver transplant patients receiving everolimus: results of a randomized, multicenter study. *Am J Transplant* 2013; 13: 1734–1745
10. Lorber MI, Mulgaonkar S, Butt KM *et al*.; B251 Study Group. Everolimus versus mycophenolate mofetil in the prevention of rejection in de novo renal transplant recipients: a 3-year randomized, multicenter, phase III study. *Transplantation* 2005; 80: 244–252
11. Cotovio P, Neves M, Santos L *et al*. Conversion to everolimus in kidney transplant recipients: to believe or not believe? *Transplant Proc* 2012; 44: 2966–2970
12. Shihab FS, Cibrik D, Chan L *et al*. Association of clinical events with everolimus exposure in kidney transplant patients receiving reduced cyclosporine. *Clin Transplant* 2013; 27: 217–226
13. Takahashi K, Uchida K, Yoshimura N *et al*. Efficacy and safety of concentration-controlled everolimus with reduced-dose cyclosporine in Japanese de novo renal transplant patients: 12-month results. *Transplant Res* 2013; 2: 14
14. Moro JA, Almenar L, Martínez-Dolz L *et al*. mTOR inhibitors and unilateral edema. *Rev Esp Cardiol* 2008; 61: 987–988
15. Fukushima N, Saito S, Sakata Y *et al*. A case of everolimus-associated chylothorax in a cardiac transplant recipient. *Transplant Proc* 2013; 45: 3144–3146
16. Ersoy A, Koca N. Everolimus-induced lymphedema in a renal transplant recipient: a case report. *Exp Clin Transplant* 2012; 10: 296–298
17. Fuchs U, Zittermann A, Berthold HK *et al*. Immunosuppressive therapy with everolimus can be associated with potentially life-threatening lingual angioedema. *Transplantation* 2005; 79: 981–983
18. Aboujaoude W, Milgrom ML, Govani MV. Lymphedema associated with sirolimus in renal transplant recipients. *Transplantation* 2004; 77: 1094–1096
19. Romagnoli J, Citterio F, Nanni G *et al*. Severe limb lymphedema in sirolimus-treated patients. *Transplantation Proc* 2005; 37: 834–836
20. Al-Otaibi T, Ahamed N, Nampoory MR *et al*. Lymphedema: an unusual complication of sirolimus therapy. *Transplant Proc* 2007; 39: 1207–1210
21. De Bartolomeis C, Collini A, Rumberger B *et al*. Generalized lymphedema in a sirolimus-treated renal transplant patient. *Clin Transplant* 2008; 22: 254–257
22. Wadei H, Gruber SA, El-Amm JM *et al*. Sirolimus-induced angioedema. *Am J Transplant* 2004; 4: 1002–1005
23. Mohaupt MG, Vogt B, Frey FJ. Sirolimus-associated eyelid edema in kidney transplant recipients. *Transplantation* 2001; 72: 162–164
24. Papali A, Giannetti N, Cantarovich M. Unilateral upper extremity edema associated with sirolimus in a heart transplant patient. *Transplantation* 2007; 83: 240–241
25. Amante AJ, Kahan BD. Technical complications of renal transplantation. *Surg Clin North Am* 1994; 74: 1117
26. Khauli RB, Stoff JS, Lovewell T *et al*. Post-transplant lymphoceles: a critical look into the risk factors, pathophysiology and management. *J Urol* 1993; 150: 22
27. Malovrh M, Kandus A, Buturovic-Ponikvar J *et al*. Frequency and clinical influence of lymphoceles after kidney transplantation. *Transplant Proc* 1990; 22: 1423
28. Bry J, Hull D, Bartus SA *et al*. Treatment of recurrent lymphoceles following renal transplantation: remarsupialization with omentoplasty. *Transplantation* 1990; 49: 477
29. Schweizer RT, Cho S, Koutz SL *et al*. Lymphoceles following renal transplantation. *Arch Surg* 1972; 104: 42
30. Braun WE, Banowsky LH, Straffon RA *et al*. Lymphocytes associated with renal transplantation: report of 15 cases and review of the literature. *Am J Med* 1974; 57: 714
31. Zincke H, Woods JE, Leary FJ *et al*. Experience with lymphoceles after renal transplantation. *Surgery* 1975; 77: 444

32. Pollak R, Veremis SA, Maddux MS *et al*. The natural history of and therapy for perirenal fluid collections following renal transplantation. *J Urol* 1988; 140: 716
33. Vitko S, Tedesco H, Eris J *et al*. Everolimus with optimized cyclosporine dosing in renal transplant recipients: 6-month safety and efficacy results of two randomized studies. *Am J Transplant* 2004; 4: 626
34. Kahan BD. Efficacy of sirolimus compared with azathioprine for reduction of acute allograft rejection: a randomized multicentre study. The Rapamune US Study Group. *Lancet* 2000; 356: 194–202
35. Sansalone CV, Aseni P, Minetti E *et al*. Is lymphocele in renal transplantation an avoidable complication? *Am J Surg* 2000; 179: 182
36. Kay R, Fuchs E, Barry JM. Management of postoperative pelvic lymphoceles. *Urology* 1980; 15: 345
37. Rashid A, Posen G, Couture R *et al*. Accumulation of lymph around the transplanted kidney (lymphocele) mimicking renal allograft rejection. *J Urol* 1974; 111: 145
38. Bischof G, Rockenschaub S, Berlakovich G *et al*. Management of lymphoceles after kidney transplantation. *Transpl Int* 1998; 11: 277
39. Stephanian E, Matas AJ, Gores P *et al*. Retransplantation as a risk factor for lymphocele formation. *Transplantation* 1992; 53: 676
40. Martinez-Ocana JC, Lauzurica R, Castellote E *et al*. Adult polycystic kidney disease: a risk factor for lymphocele formation after renal transplantation? *Transplant Proc* 1995; 27: 2246
41. Teruel JL, Escobar EM, Quereda C *et al*. A simple and safe method for management of lymphocele after renal transplantation. *J Urol* 1983; 130: 1058
42. Langer RM, Kahan BD. Incidence, therapy, and consequences of lymphocele after sirolimus-cyclosporine-prednisone immunosuppression in renal transplant recipients. *Transplantation* 2002; 27: 804
43. Pascual J, Marcén R, Ortuño J. Clinical experience with everolimus (Certican): optimizing dose and tolerability. *Transplantation* 2005; 79(Suppl): S80–S84
44. Greager MA, Dzay VJ. Vascular disease of the extremities. In: Fauchi AS, Braunwald E, Isselbacher KJ *et al.* (eds). *Harrison's Principles of Internal Medicine.* New York: McGraw-Hill 1998, 1405 pp
45. Stoeltzing O, Meric-Bernstam F, Ellis LM. Intracellular signaling in tumor and endothelial cells: the expected and, yet again, the unexpected. *Cancer Cell* 2006; 10: 89–91
46. Karkkainen MJ, Ferrell RE, Lawrence EC *et al*. Missense mutations interfere with VEGFR-3 signalling in primary lymphoedema. *Nat Genet* 2000; 25: 153–159
47. Mäkinen T, Jussila L, Veikkola T *et al*. Inhibition of lymphangiogenesis with resulting lymphedema in transgenic mice expressing soluble VEGF receptor-3. *Nat Med* 2001; 7: 199–205
48. Huber S, Bruns CJ, Schmid G *et al*. Inhibition of the mammalian target of rapamycin impedes lymphangiogenesis. *Kidney Int* 2007; 71: 771–777
49. Keogh A, Richardson M, Ruygrok P *et al*. Sirolimus in de novo heart transplant recipients reduces acute rejection and prevents coronary artery disease at 2 years: a randomized clinical trial. *Circulation* 2004; 110: 2694–2700
50. Steele GH, Adamkovic AB, Demopoulos LA *et al*. Pericardial effusion coincident with sirolimus therapy: a review of Wyeth's safety database. *Transplantation* 2008; 85: 645–647
51. Bouzas-Mosquera A, Crespo-Leiro MG, Paniagua MJ *et al*. Adverse effects of mammalian target of rapamycin inhibitors during the postoperative period after cardiac transplantation. *Transplant Proc* 2008; 40: 3027–3030
52. Agostoni A, Cicardi M. Drug-induced angioedema without urticaria. *Drug Saf* 2001; 24: 599–606
53. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin converting enzyme inhibitor therapy. A review of the literature and pathophysiology. *Ann Intern Med* 1992; 117: 234–242
54. Abbosh J, Anderson JA, Levine AB *et al*. Angiotensin converting enzyme inhibitor-induced angioedema more prevalent in transplant patients. *Ann Allergy Asthma Immunol* 1999; 82: 473–476
55. Lykavieris P, Frauger E, Habes D *et al*. Angioedema in pediatric liver transplant recipients under tacrolimus immunosuppression. *Transplantation* 2003; 75: 152–155
56. Burdese M, Rossetti M, Guarena C *et al*. Sirolimus and ACE-inhibitors: a note of caution. *Transplantation* 2005; 79: 251–252
57. Stallone G, Infante B, Di Paolo S *et al*. Sirolimus and angiotensin-converting enzyme inhibitors together induce tongue oedema in renal transplant recipients. *Nephrol Dial Transplant* 2004; 19: 2906–2908
58. Montalbano M, Neff GW, Yamashiki N *et al*. A retrospective review of liver transplant patients treated with sirolimus from a single center: an analysis of sirolimus-related complications. *Transplantation* 2004; 78: 264–268
59. Mahé E, Morelon E, Lechaton S *et al*. Angioedema in renal transplant recipients on sirolimus. *Dermatology* 2007; 214: 205–209
60. Krikorian RK, Quick A, Tal A. Angioedema following the intravenous administration of metoprolol. *Chest* 1994; 106: 1922–1923
61. Gainer JV, Nadeau JH, Ryder D *et al*. Increased sensitivity to bradykinin among African Americans. *J Allergy Clin Immunol* 1996; 98: 283–287
62. Morimoto T, Gandhi TK, Fiskio JM *et al*. An evaluation of risk factors for adverse drug events associated with angiotensin-converting enzyme inhibitors. *J Eval Clin Pract* 2004; 10: 499–509
63. Flockhart DA, Tanus-Santos JE. Implications of cytochrome P450 interactions when prescribing medication for hypertension. *Arch Intern Med* 2002; 162: 405–412
64. Lemahieu WP, Maes BD, Verbeke K *et al*. CYP3A4 and P-glycoprotein activity in healthy controls and transplant patients on cyclosporin vs tacrolimus vs sirolimus. *Am J Transplant* 2004; 4: 1514–1522
65. Barshes NR, Goodpastor SE, Goss JA. Sirolimus-atorvastatin drug interaction in the pancreatic islet transplant recipient. *Transplantation* 2003; 76: 1649–1650
66. Jeanmart H, Malo O, Carrier M *et al*. Comparative study of cyclosporine and tacrolimus vs newer immunosuppressants mycophenolate mofetil and rapamycin on coronary endothelial function. *J Heart Lung Transplant* 2002; 21: 990–998
67. Mahé E, Morelon E, Lechaton S *et al*. Cutaneous adverse events in renal transplant recipients on sirolimus-based therapy. *Transplantation* 2005; 79: 476–482

Received for publication: 4.1.14; Accepted in revised form: 16.1.14