Minireview

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

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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

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 povidone-iodine [41]. Although some patients who receive mTOR-I/PSI may develop early massive lymphocele that requires surgery, mTOR-I/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-I/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.
| Author               | Study                                         | Organ transplant         | Follow-up (months) | EVL mean level and/or mean dosage | Oedema incidence         | Control                                      |
|----------------------|-----------------------------------------------|--------------------------|--------------------|-----------------------------------|--------------------------|----------------------------------------------|
| Lehmkuhl et al. [3]  | Multicentre open-label RAD2411 study          | Heart transplant         | 12                 | 4.1 ± 1.8 ng/mL                   | EVL, 91 patients          | MMF, 83 patients                             |
|                      |                                               |                          |                    |                                   | Peripheral oedema, 39.6%  | Pericardial effusion, 36.9%                  |
|                      |                                               |                          |                    |                                   | Pleural effusion, 24.2%   | EvL+, 140 (29.3%)                           |
|                      |                                               |                          |                    |                                   | EvL−, 142 (8.5%)          |                                             |
| Gullestad et al. [4] | Multicentre randomized trial                  | Heart (n=190) and lung   | 12                 | 3–8 ng/mL                        | EVL+, 103 (8.3%)          | EVL−, 119 (8.7%)                            |
|                      |                                               | (n=92) transplant        |                    |                                   |                          |                                             |
| Gullestad et al. [5] | Multicentre randomized trial                  | Heart (n=190) and lung   | 24                 | 4.5 ± 1.4 ng/mL                   | EVL−, 142 (8.5%)          |                                             |
|                      |                                               | (n=92) transplant        |                    |                                   |                          |                                             |
| 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 trial, H2304 study group| Liver transplant         | 12                 | 6–10 ng/mL                       | EVL−, 142 (8.5%)          |                                             |
| Alegre et al. [8]    | Retrospective                                | Liver transplant         | 48                 | 5.5 ± 2.2 ng/mL                   | EVL overall, 13/57 (28.8%)|                                             |
| Saliba et al. [9]    | Randomized controlled trial, H2304 study group| Liver transplant         | 24                 | AE                                | EVL− reduced TAC, 6/245 (2.4%)| TAC elimination, 42/231 (18.3%) |
|                      |                                               |                          |                    | Ascites                           | EVL− reduced TAC, 11/245 (4.5%)| TAC control, 26/243 (10.8%)               |
|                      |                                               |                          |                    | Peripheral oedema                 | EVL− reduced TAC, 55/245 (22.4%)| TAC elimination, 45/231 (19.7%) |
|                      |                                               |                          |                    | Pleural effusion                  | EVL− reduced TAC, 15/245 (6.1%)| TAC control, 36/243 (14.9%)               |
|                      |                                               |                          |                    |                                   |                          | 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%)                        |
| Cotovio et al. [11]  | Retrospective register-based study           | Kidney transplant        | 6                  | EVL 3 mg/d                        | 92/191 (47.4%)            | MMF, 82/196 (41.8%)                        |
| Shihab et al. [12]   | Randomized controlled trial                  | Kidney transplant        | 12                 | 5.9 ± 2.6 ng/mL                   | 8 (5.3%)                 |                                             |
|                      |                                               |                          |                    | <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.
| Reference | Organ transplant | mTOR-I/PSI | 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 | Stop | Partial resolution 2 months after |
|           |                 | Switch to SRL, 1 mg/day | 10 ng/mL | Few days | Increase in the oedema | | |
| [15]      | Heart           | EVL, re-introduction of EVL (TCAV progression) | NA | 36 months | Bilateral chylothorax | Switch EVL to MMF | Complete resolution within 8 months |
|           |                 | EVL, 0.5 mg/day | 5 ng/mL | 1 month | Hand and forearms | Partial resolution | Complete resolution |
|           |                 | Switch to SRL, 1 mg/day | 10 ng/mL | Few days | Increase in the oedema | Stop | Complete resolution |
| [16]      | Kidney          | EVL, 0.5–1 mg/day (6 patients) | >3 ng/mL | 12 months | Feet oedema | No | |
|           |                 | EVL, 1.5 mg/day | 3–8 ng/mL | 2–41 days | AE | IV prednisone and clemastin | Complete resolution |
|           |                 | EVL, dosage NA | NA | 3 months | Mild oedema on both legs, LUE and left breast, recurrent lymphangitis | SRL discontinuation | Complete resolution within few months |
|           |                 | EVL, dosage NA | NA | 6 months | Mild oedema on both legs and redness of RUE and right breast, Oedema both legs, nephrotic syndrome | SRL discontinuation | Complete resolution within few months |
|           |                 | EVL, dosage NA | NA | 4 months | | | Partial resolution, 60–70% within few months |
| [19]      | Kidney          | SRL, 9.5 mg/day | 26.3 ng/mL | 36 months | Severe oedema and redness of LUE and left breast, Oedema both legs, recurrent lymphangitis | Reduction of SRL dosage (trough levels of 5–10 ng/mL) | Complete resolution |
|           |                 | 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% |
|           |                 | SRL, 2 mg/day | 10–18 ng/mL | 30 months | | SRL withdrawal | Significant improvement |
|           |                 | SRL, 3 mg/day | 10–15 ng/mL | 30 months | | SRL withdrawal | Significant improvement within few months |
|           |                 | SRL, 3 mg/day | 10–18 ng/mL | 24 months | | 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 |
|           |                 | 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 |
|           |                 | SRL, 8 mg/day | 19.5 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 6 weeks after |
|           |                 | 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 (GjL)—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 (AIIRRA), 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 initiate of mTOR-I/PSI therapy. Drug trough level at presentation after adequate therapy of the symptoms. The recurrence after adequate therapy of the symptoms. The responsibility of mTOR-I/PSI in the pathogenesis of AE is suggested either as the sole oetiological 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-intensive investigations for patients showing this symptom during treatment with mTOR-I/PSI.

Conflict of interest statement. None declared.

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