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The Future of Lymphedema: Potential Therapeutic Targets for Treatment

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Abstract

Purpose of Review This review aims to summarize the current knowledge regarding the pharmacological interventions studied in both experimental and clinical trials for secondary lymphedema.

Recent Findings Lymphedema is a progressive disease that results in tissue swelling, pain, and functional disability. The most common cause of secondary lymphedema in developed countries is an iatrogenic injury to the lymphatic system during cancer treatment. Despite its high incidence and severe sequelae, lymphedema is usually treated with palliative options such as compression and physical therapy. However, recent studies on the pathophysiology of lymphedema have explored pharmacological treatments in preclinical and early phase clinical trials.

Summary Many potential treatment options for lymphedema have been explored throughout the past two decades including systemic agents and topical approaches to decrease the potential toxicity of systemic treatment. Treatment strategies including lymphangiogenic factors, anti-inflammatory agents, and anti-fibrotic therapies may be used independently or in conjunction with surgical approaches.

Keywords Lymphedema · TH2 cells · CD4 + · VEGF-C · TGFB · Non-steroidal anti-inflammatory drugs · NSAID · Doxycycline · Tacrolimus · ACE inhibitors · Captopril · Pirfenidone · Tetracyclines · Vascular endothelial growth factor C

Introduction

Lymphedema is a progressive disease that causes tissue swelling, fluid accumulation, and chronic fibroadipose tissue deposition [1]. Lymphedema can be categorized based on the etiology of the disease. Patients with primary lymphedema have genetic abnormalities of the lymphatic system that manifest as tissue swelling, chylothorax, or chylous ascites in utero, shortly after birth, or at some point in the patient's life. Secondary lymphedemas are caused by external insults such as infections, radiation, obesity, or iatrogenic injury to the lymphatic system during the course of oncologic surgery [2, 3]. Breast cancer, due to the high prevalence of this disease, is the most common cause of secondary lymphedema in developed countries. Approximately 1 in 3 patients who undergo axillary lymph node dissection

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(ALND) and 3–5% of the patients treated with sentinel lymph node biopsy (SLND) develop breast cancer–related lymphedema (BCRL) [4–7]. Lymphedema also develops in approximately 1 in 6 patients treated for other solid tumors such as melanoma, gynecological or urological tumors, or sarcomas [8]. Although the estimated number of patients who suffer from lymphedema in the USA is unknown, analysis of the incidence of the disease and cancer survival rates suggest that approximately 1 million American cancer survivors suffer from secondary lymphedema.

Patients with lymphedema have decreased quality of life (QoL) and often complain of pain and functional problems [1, 5, 9–14]. Nearly 40% of patients with lymphedema also develop recurrent infections which, in some cases, can be quite severe resulting in sepsis and hospitalization for intravenous antibiotics. Treatment of lymphedema is time intensive and not always covered by insurance resulting in significant financial toxicity [12, 15, 16]. Despite the high incidence and severe sequelae of lymphedema, the disease is incurable and primarily treated palliatively with compression garments and manual lymphatic drainage [1, 17–20]. Surgical options have been developed in the past decade; however, the success rates of these treatments are variable, and most patients still require compression after surgery [1, 21, 22]. Therefore, developing effective treatment strategies for lymphedema is an important unmet clinical need.

This review aims to summarize the current knowledge regarding the pharmacological interventions in experimental and clinical trials for secondary lymphedema (Table 1) [23–28]. The first section reviews systemic treatments, and the second section summarizes topical approaches.

Systemic Treatments for Secondary Lymphedema

Lymphangiogenic Factors

Vascular endothelial growth factor C (VEGF-C) is a high-affinity ligand for the tyrosine kinase receptor VEGFR3. VEGFR3 is expressed primarily by lymphatic endothelial cells (LECs) and regulates important functions such as lymphatic vessel sprouting, LEC proliferation, migration, differentiation, and expression of endothelial nitric oxide synthase (eNOS) [1, 29–36]. Delivery of VEGF-C using an adenoviral vector to mice with primary lymphedema resulting from a heterozygous inactivating *Vegfr-3* mutation increases lymphangiogenesis and decreases tissue swelling [37]. These findings were supported by studies in a rabbit ear model of secondary lymphedema in which injection of recombinant VEGF-C into the surgical bed increased lymphangiogenesis, restored normal lymphatic function, and decreased the severity of ear swelling compared with control animals [38–40]. Other groups incorporated recombinant VEGF-C in nanofibrillar collagen scaffolds to support collateral lymphatic formation across the obstructed area (BioBridge™) [41]. Animals treated with the device had decreased extracellular fluid accumulation 3 months after surgery. In follow-up animal studies, treatment with BioBridge resulted in increased collateral lymphatic formation toward other lymph node drainage basins as well as decreased edema 4 months after surgery [42]. Using the BioBridge in patients treated with vascularized lymph node transplantation (VLNT) or lymphovenous bypass (LVB) improved lymphatic drainage and decreased swelling [43]. Another retrospective study of 29 patients treated with BioBridge and VLNT also showed an increase in the number of lymphatic collectors and a decrease of dermal backflow 1 year after surgery [44].

Due to the high costs of recombinant VEGF-C, gene therapy was explored to increase VEGF-C expression. Yoon et al. utilized a naked plasmid technique to transfer plasmid DNA encoding human VEGF-C to a rabbit ear model. This study yielded similar results to treatment with recombinant VEGF-C injection decreased dermal thickening and improvement in lymphatic pumping [45]. VEGF-C gene therapy successfully increased the expression of lymphangiogenic markers like VEGFR-3, improving lymphatic vessel growth and lymphatic drainage [45, 46].

Viral vectors for VEGF delivery were also developed by several groups. These included a VEGFR3-specific VEGF-C isoform (VEGF-C156S) delivered using an adeno-associated viral (AAV) vector enabling long-term delivery [47, 48]. AAV-VEGF-C administration to the site of surgical injury increased lymphatic capillary regrowth and lymph vessel maturation in animal models [49, 50]. In humans, the efficacy of Lymfactin®, an investigational adenoviral type-5-based gene therapy vector encoding expression of human VEGF-C, has been studied in phase I and II clinical trials in conjunction with VLNT treatment [51–53]. No adverse events were reported at 24-month follow-up in a phase I clinical trial of 15 breast cancer–related upper limb lymphedema (BCRL) patients (NCT02994771). In the higher dose group, a 46% reduction in excess arm volume was demonstrated at 12 months after surgery alongside significant improvement of quality of life scores [53]. However, the results of a phase II double-blind, randomized, placebo-controlled, multicenter clinical trial (NCT03658967) were inconclusive, and development of the drug was stopped [52].

The use of *mRNA therapeutics* is an evolving area of gene delivery therapy that has gained increased interest since the COVID-19 pandemic [54, 55]. Nucleoside-modified mRNA encapsulated in lipid nanoparticles (LNPs) encoding VEGF-C stimulates lymphatic growth in a mouse lymphedema model [56]. A single injection of low-dose VEGF-C mRNA-LNPs resulted in sustained VEGF-C levels for as long as 60 days after treatment, stimulated site-specific lymphatic

Table 1 Pharmacological interventions for the treatment of lymphedema

Type of intervention	Proposed mechanism for lymphedema treatment	Authors, publication year
Systemic interventions		
VEGF-C	*Lymphangiogenesis*	Szuba et al., 2002
Subcutaneous injection	VEGF-C directly binds VEGFR-3 to activate intracellular signaling pathways that promote LEC growth and survival	
VEGF-C Naked plasmid technique	*Lymphangiogenesis* Transfer of plasmid DNA encoding VEGF-C increases VEGFR-3 expression and activation	Yoon et al., 2003
VEGF-C Viral vectors: Adenovirus ---Lymfactin® Adeno-Associated	*Lymphangiogenesis* Adenoviral and adeno-associated gene vectors encoding VEGF-C regenerate lymphatic vessels and preserve lymphatic architecture post VLNT	Lai et al., 2002 Tammela et al., 2007 Hartiala et al., 2020
VEGF-C mRNA vectors	*Lymphangiogenesis* Nucleoside-modified mRNA encoding VEGF-C stimulates site-specific lymphatic growth at low dosages	Pardi et al., 2018 Brown et al., 2020 Szöke et al., 2021
Hepatocyte growth factor (HGF)	*Lymphangiogenesis* VEGFR-3 independent stimulation of LEC proliferation and migration	Kajiya et al., 2005 Wong et al., 2021
9-cis retinoic acid (RA)	*Lymphangiogenesis* Indirect activation of PI3K/Akt pathway via fibroblast receptor signaling to stimulate LEC proliferation	Choi et al., 2012 Wong et al., 2021
Adipose-derived stem cells (ADSCs)	*Lymphangiogenesis* ADSCs release a secretome of bioactive factors that reinforce LEC growth and survival	Hwang et al., 2011 Ahmadzadeh et al., 2020 Yan et al., 2011
Ketoprofen (NSAID)	*Anti-inflammatory* 5-Lipoxygenase (5-LO) inhibition, ↓ leukotriene B4 (LTB4) synthesis	Nakamura et al., 2009 Tian et al., 2017 Rockson et al., 2018
Bestatin (NSAID)	*Anti-inflammatory* Leukotriene A4-hydrolyase (LTA4H) inhibition, ↓ leukotriene B4 (LTB4) synthesis	Tian et al., 2017 Cribb et al., 2021
Fingolimod (Gilenya®)	*Anti-inflammatory* Inhibition of activated CD4 + T cell emigration from LNs impairs TH2 differentiation	García Nores et al., 2018
Neutralizing antibodies	*Anti-inflammatory* Th2 inflammatory cytokine blockade (IL-4/IL-13 inhibition)	Avraham et al., 2013 Savetsky et al., 2015 Mehrara et al., 2021
Doxycycline	*Anti-inflammatory* Inhibition of Th2 phenotype differentiation, ↓ monocyte recruitment, ↓ polarization of alternatively activated M ϕ	Debrah et al., 2006 Mand et al., 2012 Furlong-Silva et al., 2021 Brown et al., 2023
Anti-transforming growth factor beta-1 (TGF- β1)	*Anti-fibrotic* Inhibition of TGF-β1 disrupts fibroblast maturation to myofibroblasts, improving lymphostatic fibrosis	Meng et al., 2016 Yoon et al., 2020
Topical interventions		
hADSCs and VEGF-C hydrogel	*Lymphangiogenesis* hADSC mediated sustained release of VEGF-C	Hwang et al., 2011
Recombinant human fibroblast growth factor 2 (FGF2)	*Lymphangiogenesis* ↑ VEGF-C and VEGF-D expression	Onishi et al., 2014
Tacrolimus	*Anti-inflammatory* Inhibition of IL-2-mediated CD4 + T cell activation/differentiation	Gardenier et al., 2017 Gulmark Hansen et al., 2023
Pirfenidone	*Anti-fibrotic* Inhibition of TGF-β1	Baik et al., 2022
Captopril	*Anti-fibrotic* ACE inhibitor—inhibition of intracellular TGF-β1 signaling pathways	Brown et al., 2023

Abbreviations: *VEGF* vascular endothelial growth factor, *VEGFR* vascular endothelial growth factor receptor, *LEC* lymphatic endothelial cell, *DNA* deoxyribonucleic acid, *VLNT* vascularized lymph node transplant, *mRNA* messenger ribonucleic acid, *IL* interleukin, *hADSCs* human adipose-derived stem cells

growth, restored lymphatic function, and reversed clinical signs of lymphedema [56].

Other lymphangiogenic factors such as *hepatocyte growth factor* (HGF) and retinoic acid agonist *9-cis retinoic acid (9-cRA)* also have therapeutic potential in preclinical models of lymphedema [57–61]. Treatment of cultured lymphatic endothelial cells (LECs) with HGF increases proliferation, migration, and lymphatic tubule formation, independent of the VEGFR-3 pathway [62]. 9-cRA, a derivative of vitamin A, stimulates LEC differentiation, migration, and collateral lymphatic formation in part by activating fibroblast receptor signaling and by downregulating expression of cell cycle inhibitors P27 and p57 [60, 61, 63–66].

Anti-inflammatory Agents

Non-steroidal Anti-inflammatory Drugs (NSAID)

Rockson and colleagues demonstrated the important role of inflammation in the pathophysiology of lymphedema and showed that *ketoprofen*, a non-steroidal anti-inflammatory (NSAID) drug, decreases inflammation, improves dermal-epidermal architecture, decreases swelling, and increases collateral lymphatic formation in the mouse tail model [67, 68]. Ketoprofen also significantly decreased expression of inflammatory cytokines (TNF-α and MCP-1) and increased expression of VEGF-C. Ketoprofen was used in a clinical trial (NCT02257970) in patients with primary or secondary lymphedema of the upper or lower extremities [69]. In the early phases of the study, 21 patients with lymphedema were enrolled in an open-label trial in which 75 mg ketoprofen was orally administered 3 times daily for a duration of 4 months [69]. Treatment with ketoprofen resulted in dermal thickness and collagen deposition and decreased perivascular inflammation compared to pretreatment skin biopsies. No changes in limb volume or bioimpedance were noted. The authors then conducted a randomized placebo-controlled trial with 34 patients (16 treated with ketoprofen for 4 months vs. 18 placebo controls) with upper/lower extremity lymphedema. These studies also showed improved skin changes (e.g., dermal thickness) and decreased expression of systemic inflammatory markers such as granulocyte colony-stimulating factor (G-CSF). However, as with the non-randomized trial, no significant changes in limb volume or bioimpedance were noted.

Follow-up studies by Rockson's group found that the beneficial effects of ketoprofen are attributed to its inhibition of the 5-lipoxygenase pathway (5-LOX) metabolite, leukotriene B4 (LTB_4) [70]. These findings led to another randomized clinical trial (NCT02700529) with bestatin (Ubenimex), a selective LTB_4 antagonist. A cohort of 146 lower extremity lymphedema patients were treated three times daily for 6 months with bestatin. The results of this trial were inconclusive, and larger trials are planned [71].

Tetracyclines

Tetracycline antibiotics (e.g., doxycycline) have been used to treat patients with chronic filarial secondary lymphedema and decrease limb and tissue swelling independent of their antibiotic effects [72–7677••]. A double-blind, placebo-controlled trial in Ghana evaluated lymphedema outcomes in patients with bancroftian filariasis who were treated with a 6-week regimen of 200 mg/day doxycycline and anti-parasitic therapy vs. anti-parasitic treatments alone (ISRCTN 14,757) [73]. Lymphedema outcomes were measured at 12- and 24-month time points and showed decreased serum levels of VEGF-C and soluble VEGFR3 levels, as improved skin texture and skin crease character. These findings prompted a larger randomized study with 3 treatments arms to compare the efficacy of 6-week courses of amoxicillin (1000 mg/day), doxycycline (200 mg/day), or placebo in 164 patients with mild-to-moderate filarial lymphedema (ISRCTN 90,861,344) [74]. At 12- and 24-month follow-up intervals, 44% of doxycycline patients had decreased skin thickness and swelling compared to only 3.2% and 5.6% of amoxicillin and placebo groups, respectively. Based on these results, the authors reached a consensus recommending a 6-week course of doxycycline treatment once a year or every other year for patients with mild-to-moderate filarial lymphedema [74]. Recent findings of a retrospective analysis by our group in 17 patients with breast cancer–related lymphedema (BCRL) showed improvements in patient-reported quality of life following treatment with a 6-week course of doxycycline (200 mg/day) [78]. However, in contrast to the studies in filariasis, we found no differences in limb volume or bioimpedance suggesting that larger studies may be needed.

Neutralizing Antibodies

Neutralizing antibodies have revolutionized treatment of chronic inflammatory disorders by causing targeted reductions in inflammatory responses and resultant decreased systemic toxicity. Our lab has previously shown that Th2 immune responses play a key role in the pathophysiology of lymphedema [79–81]. Based on these findings, we conducted a phase I open-label clinical trial (NCT02494206) evaluating the efficacy of anti-IL4/IL13 neutralizing antibodies in the management of unilateral BCRL. Nine women with stage I/II BCRL were treated with once-monthly injections of QBX258, a drug consisting of humanized monoclonal antibodies against IL-4 (VAK296) and IL-13 (QAX576) for 4 months [82••]. QBX258 treatment was safe with most reported adverse events being minor and self-limited in nature. Anti-IL4/IL13 neutralizing antibody treatment resulted in improved histologic appearance of lymphedematous tissues, reduced skin stiffness, and improved QoL outcome measures. Therapy with compound QBX258 significantly attenuated keratinocyte hyperplasia, mast cell

infiltration, and Th2-related cytokine expression within the skin. However, we found no significant improvements in arm volumes or bioimpedance. Future, larger studies possibly with more targeted anti-Th2 therapies are needed and planned.

Topical Treatments for Secondary Lymphedema

Lymphangiogenic Factors

Topical formulations of recombinant human VEGF-C have been developed to ensure sustained release and to avoid direct injection [38]. Hwang and colleagues used a gelatin hydrogel containing VEGF-C at the site of tissue injury in a lymphedema mouse model [83]. Mice treated with both implanted human adipose-derived stem cells (hADSCs) and VEGF-C hydrogel had decreased dermal edema and improved lymphatic regeneration compared to the controls treated with just hADSCs or VEGF-C alone.

Fibroblast growth factor 2 (*FGF2*) promotes lymphangiogenesis via induction of VEGF-C and VEGF-D [84]. Onishi et al. used topical basic fibroblast growth factor (bFGF) to treat secondary lymphedema in a rat tail model [85]. Treatment with topical bFGF increased expression of VEGF-C/D, increased lymphatic vessel density, decreased tail swelling, and improved lymphatic function.

Anti-inflammatory Agents

Tacrolimus

Tacrolimus is a macrolide calcineurin inhibitor with anti-T-cell activity. FDA-approved for treating cutaneous inflammatory conditions, topical tacrolimus administration inhibits $CD4^+$ cell proliferation and differentiation by inhibiting IL-2 [86–94]. Topical administration of tacrolimus decreases inflammation, Th2 cytokines, fibroadipose tissue deposition, swelling, and improves lymphatic function in mouse models of lymphedema [95]. Topical application of tacrolimus, unlike oral administration, did not result in significant systemic absorption and had no significant systemic anti-inflammatory effects [91]. A recent open-label, single-arm, phase II trial (NCT04541290) demonstrated that a 6-month treatment course with topical tacrolimus significantly improved limb volumes, bioimpedance scores, and quality of life scores in eighteen women with BCRL. However, assessment of lymphatic function using ICG lymphography was inconclusive [96].

Anti-fibrotic Therapies

Dermal fibrosis is a histological hallmark of lymphedema, and the degree of fibrosis positively correlates with the severity of lymphedema [97–99]. Progressive fibrosis results in lymphatic obstruction perpetuating the cycle of fluid accumulation, inflammation, and fibrosis. Transforming growth factor beta-1 (*TGF-β1*) is a key regulator of fibrosis in a variety of organ systems [99, 101, 102100••,]. Using a rat hindlimb model of secondary lymphedema, Sano et al. found that the TGF-β1/Smad signaling pathway is responsible for the early to late changes of fibrosis that is seen in lymphedema patients. We have shown that the expression of TGF-B1 and its downstream mediators is markedly increased in skin biopsies collected from patients with stage II/III BCRL [100••]. Other studies have shown that inhibiting TGF-β1 activity with a small-molecule inhibitor improves radiation-induced fibrosis and lymphatic dysfunction [103]. Blockade of TGF-β1 signaling using neutralizing antibodies decreases fibrosis, increases collateral lymphatic formation, and decreases the pathophysiology of lymphedema in preclinical mouse models [102, 104, 105]. TGF-β1 in lymphatic fluid increases stiffness and proliferation of fibroblasts, LECs, and lymphatic smooth muscle cells (LSMCs). Topical application of pirfenidone (PFD), a small-molecule inhibitor approved by the US Food and Drug Administration (FDA) for the treatment of idiopathic pulmonary fibrosis, decreases TGF-β1 signaling, fibrosis, and the pathophysiologic findings of lymphedema in mouse models.

TGF-B1 activity in cardiac, renal, and hepatic fibrosis is modulated by tissue activity of tissue-specific renin-angiotensin system [106–115]. Expression of angiotensin-converting enzyme in these tissues drives the conversion of angiotensin I (Ang I) to angiotensin II (Ang II). AngII is a key regulator of fibrosis by modulating intracellular TGF-B1 activity and downstream signaling. ACE inhibitors or Ang II receptor antagonists inhibit fibrosis by decreasing TGF-β1 activity in cardiac, renal, and hepatic models of fibrosis [106–115]. We have recently shown that the expression of ACE and AngII is increased in clinical lymphedema biopsy specimens [116]. Topical captopril treatment in mouse models of lymphedema resulted in decreased fibrosis, inhibition of intracellular TGF-β1 signaling pathways, decreased inflammation, and decreased swelling.

Conclusions

Many potential treatment options for lymphedema have been explored throughout the past two decades including systemic agents and topical approaches to decrease the potential toxicity of systemic treatment. Treatment strategies including lymphangiogenic factors, anti-inflammatory agents, and anti-fibrotic therapies may be used independently or in conjunction with current surgical approaches. Larger studies with better methodological design and standardized outcome measures are needed to define the role of these strategies in the clinical setting.

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Declarations

Conflict of Interest Babak J. Mehrara, MD, is the recipient of investigator-initiated research grants from PureTech and Regeneron and has received royalty payments from PureTech; he also has served as a consultant for Pfizer Corp.
Joseph H. Dayan, MD, is a paid consultant for the Stryker Corporation, has intellectual property rights with Elucida Oncology and equity interest in Welwaze Medical, LLC, and has a royalty agreement with Springer Publishers for Multimodal Management of Upper and Lower Extremity Lymphedema. All other authors report no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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