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CANCER REHABILITATION (SR SMITH, SECTION EDITOR)

Molecular and Biologic Targets for Radiation Fibrosis: Implications for Rehabilitation

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Abstract

Purpose of Review The purpose of this article is to describe the pathophysiology of radiation fibrosis (RF) as well as highlight and review the evidence for novel molecular and biologic targets under investigation to address RF. This article also summarizes the treatment paradigms for radiation fibrosis syndrome (RFS) involved in comprehensive cancer rehabilitation.

Recent Findings Recent preclinical studies have investigated various agents targeting transforming growth factor-beta (TGF-β) and platelet-derived growth factor (PDGF), many of which showed favorable outcomes. However, results have been mixed and suggest potential for tissue-specific results. In a small pilot study, pirfenidone was found to improve symptoms. The combination of pentoxifylline and vitamin E has been utilized clinically and has mixed results in the literature.

Summary RF is progressive sclerosis of tissue that results in a myriad of clinical manifestations referred to as RFS. The pathophysiology of RF is multifaceted involving multiple molecular pathways. Molecular and biologic targets involved in these pathways are under investigation. Most remain in preclinical stages, and many have mixed results. Given the dearth of clinically available treatments for RF, cancer rehabilitation is essential to help ameliorate symptoms as well as optimize and maintain function and quality of life.

Keywords Radiation fibrosis · Cancer · Radiation therapy

Introduction

As cancer treatments have evolved, the number of cancer survivors continues to increase [1]. Radiation therapy is a treatment modality commonly used to manage many cancers, including head and neck, breast, prostate, and lymphoma, as part of curative or palliative intent. It is projected that the number of cancer survivors treated with radiation therapy will continue to increase [2]. To meet the needs of this growing population, increased attention to the late effects of radiation is necessary. Although radiation therapy is an effective treatment modality for many forms of cancer, it can also result in several acute and late effects, including radiation fibrosis (RF). The late effects of RF may present months to years following completion of treatment and are chronic and progressive. RF can impact any tissue and result in functional impairments and decreased quality of life [3]. Depending on the tissues involved, a myriad of clinical manifestations of RF may occur. Within the neuromuscular system, this may include cervical dystonia, trismus, dropped head syndrome, shoulder dysfunction, and myelo-radiculo-plexo-neuro-myopathy [4]. RF can also impact the visceral tissues, including pulmonary, cardiac, gastrointestinal, and integumentary systems [5•].

Treatment and patient-specific risk factors for RF have been identified. Treatment-related factors include total dose of radiation, dose per fraction, volume of tissue treated, tissue type treated, prior radiation, and additional treatment modalities [6]. Patient-specific factors include genetics, pre-existing peripheral nervous system dysfunction, or connective tissue disease [7]. Advances within the field of radiation oncology have mitigated damage to healthy tissue by using three-dimensional conformation techniques and intensity modulated therapy [8, 9]. Earlier identification and intervention for RF can help ameliorate and preserve function. There is also data suggesting that radiation-induced late toxicity may in part be reversible with pharmacologic interventions which we will discuss below [10]. For individuals presenting to cancer

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rehabilitation physicians with functional impairments related to RF, it is valuable to understand the pathophysiology, current treatment paradigms, and emerging treatments to prevent, attenuate, and treat RF to optimize function and improve quality of life.

There is an extensive list of potential late effects of radiation, and there is currently no cure for the progressive sclerosis of radiation fibrosis syndrome (RFS) [11]. However, through comprehensive cancer rehabilitation interventions and partnering with patients, we can provide hope for goals towards optimizing and maintaining function and quality of life. Management of RF must include patient education, therapy interventions, and lifelong home exercise. Additional interventions can include orthotics, assistive devices, pain control, injection procedures, and pharmacotherapy. Furthermore, emerging in the literature are novel investigations into targets to prevent, mitigate, and improve RF. This article will highlight the pathophysiology of RF and explore novel biologic and molecular targets under investigation and the implications for rehabilitation.

Pathophysiology

RF describes the insidious, progressive, immortalized, pathologic tissue sclerosis that occurs in response to ionizing radiation delivered to the tissues as part of the treatment paradigm for various cancers. RFS describes the multiple clinical sequelae that occur as a result of RF. Late effects of radiation can occur in any body tissue including nerve, muscle, bone, fascia, ligament, tendon, skin, and viscera [4, 5•].

The exact mechanisms for RF are not completely understood. There are multiple molecular pathways that have been proposed, and the pre-eminent pathways vary slightly depending on the tissue irradiated (i.e., cardiac, pulmonary, gastrointestinal, integumentary, endocrine, vascular, lymphatic, neuromuscular, etc.). However, taken altogether, they are thought to result in the clinical manifestation of RFS. The pathways this article will focus on can be subdivided and defined as follows: the reactive oxygen species (ROS) pathway; the DNA damage response (DDR) pathway; the transforming growth factor-beta (TGF-β) pathway; the inflammatory cytokine/chemokine (ICC) pathway involving multiple cytokines, chemokines, interleukins, and more; and the fibroblast/myofibroblast proliferation (FMP) pathway. These intricate pathways are illustrated in Fig. 1.

In the ROS pathway, it is theorized that ionizing radiation causes lysis of water molecules into superoxide, hydrogen peroxide, and hydroxyl radicals which go on to cause direct DNA damage and upregulation of the p16 pathway that results in cell senescence and apoptosis [6, 12•]. The DDR pathway leads to a similar result; however, it does so through ataxia telangiectasia-mutated (ATM) protein nucleo-shuttling and upregulation of p53/p21 cell senescence/apoptotic pathways as well as direct radiation-induced DNA damage resulting in cell death [12•, 13]. The ICC pathway, which closely follows the above early pre-fibrotic phase pathways, comprised leukocyte response to endothelial damage from ionizing radiation [14, 15••]. When circulating leukocytes then move into the extracellular matrix (ECM), they release a wide range of pro-inflammatory cytokines and chemokines including TNF-α and TGF-β, various interleukins, and platelet-derived growth factor (PDGF). PDGF along with other various interleukins serve to recruit stromal fibroblasts and promote differentiation of circulating mesenchymal stem cells (MSCs) into fibroblasts [6, 14, 15••]. For the TGF-β pathway, the previously aforementioned free radical part of the ROS pathway upregulates the release of TGF-β which, along with direct release of TGF-β from leukocytes in response to the presence of apoptotic cells, leads to further recruitment of fibroblasts and promotion of differentiation of recruited fibroblasts into myofibroblasts within the extracellular matrix [6, 15••, 16]. With the overwhelming recruitment of fibroblasts and differentiation of myofibroblasts in this intermediate constitutive organized fibrosis phase, the FMP pathway finally takes the lead. Secretion of basic fibroblast growth factor (bFGF) follows, which leads to endothelial cell proliferation, angiogenesis, and excess deposition of collagen into the extracellular matrix [6, 15••, 17]. This gradually results in local tissue ischemia over time and retractile fibrosis, closing out the late fibroatrophic phase.

Targets

The pathophysiology of RF, as described above, is complex and multifactorial. As such there are numerous targets being investigated for potential therapeutic strategies to prevent, mitigate, or treat RF. These are summarized in Table 1. To fully describe each of these is beyond the scope of this article, but we will review a selection of these targets in more detail. Targeting RF at the cellular level has implications for the functional impairments patients may develop, and rehabilitation physicians may be the providers to administer some of these treatments.

TGF-β has an integral role in the fibrosis pathway, making it a strategic target for several investigational interventions. As a result of radiation, TGF-β is upregulated and increases the pro-fibrosis pathways of Smad2/3 and Rho/Rock. LY2109761 is a small molecule that inhibits TGF-β receptor 1 and has been found to decrease inflammation and pulmonary fibrosis in mice models [18]. Further study in vitro and ex vivo (human and rat liver slices) found that LY2109761, in addition to affecting TGF-β, has antifibrotic effects by downregulating gene expression of the inhibitor of metalloproteinase 1 and Smad2 protein phosphorylation [19]. Halofuginone,

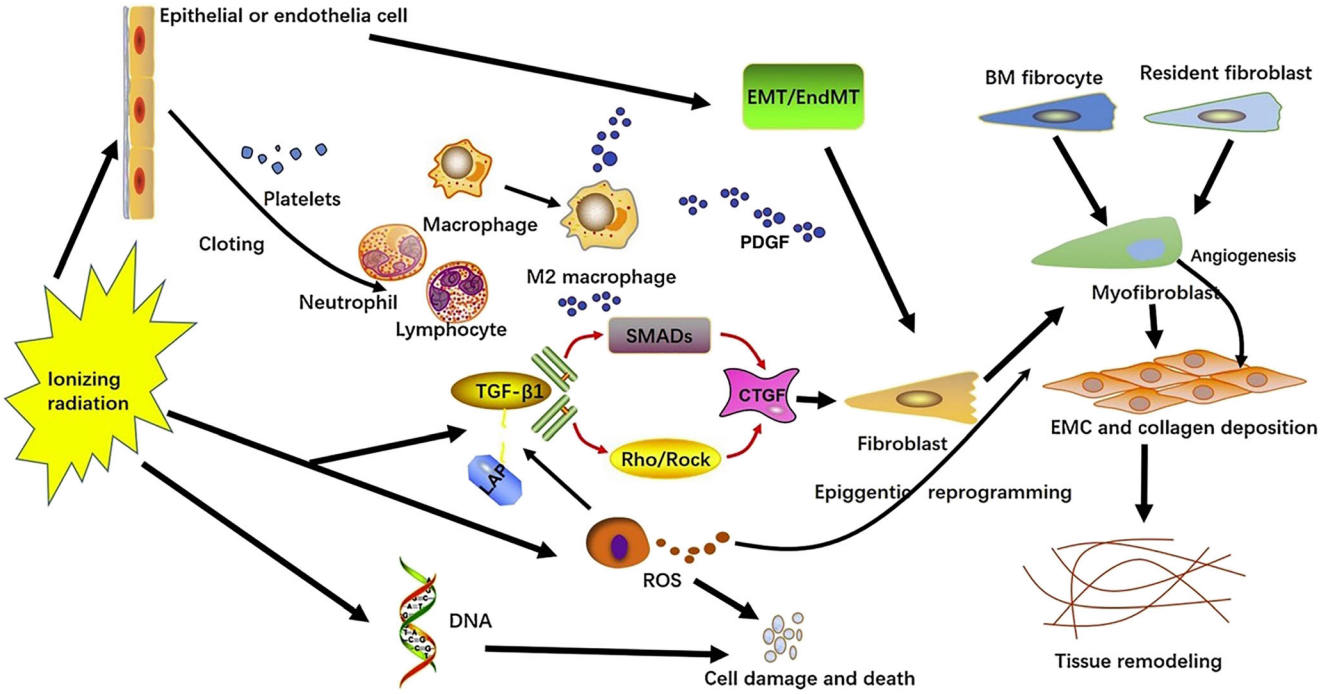

Fig. 1 Illustration of complex, interconnected molecular pathways resulting in radiation fibrosis Reprinted from Wang et al [15••] with minor revision (https://creativecommons.org/licenses/by/4.0/)

a TGF-β receptor 2 blocker, has been shown to lessen radiation-induced fibrosis in mice [20], protect against radiation-induced leg contraction in mice [21], and ameliorate radiation-induced lung injury in rats [22]. Thalidomide is another agent with potential to address fibrosis. One study found that thalidomide alleviated radiation-induced lung fibrosis [23] by down-regulating the TGF-β/Smad3 signaling pathway in mice, but another study found that it did not reduce radiation-induced heart disease in mice [24]. These two studies highlight mixed results and suggest possible tissue-specific effects.

Platelet-derived growth factor (PDGF) is another potential target for intervention, and there is evidence that PDGF receptor tyrosine kinase inhibitors can mitigate fibrosis. SU9518 and imatinib are PDGF receptor tyrosine kinase inhibitors that were found to decrease the development of radiation-induced pulmonary fibrosis in mice [25]. SU9518 was found to reduce radiation-induced fibroblast and endothelial cell activation [26]. Imatinib inhibits tyrosine kinases of the TGFβ and PDGF pathways and has been shown to mitigate radiation-induced lung fibrosis in mice [27] and inhibit radiation-induced dermal fibrosis [28]. However, it did not attenuate ovarian tissue fibrosis in rats [29]. Again, these mixed results may indicate tissue-specific outcomes. In addition to targeting PDGF or TGF-β individually, Dadrich et al showed that combined inhibition was more efficacious in decreasing radiation-induced lung fibrosis in mice [30].

Pirfenidone is another antifibrotic agent currently FDA approved for idiopathic pulmonary fibrosis. It acts as a regulator of cytokine expression that suppresses the TGF-β1/Smad/CTGF pathway, as well as PDGF and TNF-α, inhibiting fibroblast proliferation. Investigation into its benefit in RF is ongoing. It was found to mitigate radiation-induced intestinal fibrosis in rat models [31] and radiation-induced pulmonary fibrosis in mice [32, 33]. A small pilot study with seven participants with a history of head and neck cancer or Hodgkin's lymphoma found several patients experienced improvement in their range of motion and all reported a subjective improvement in their symptoms [34]. However, two participants were withdrawn due to a possible adverse event of syncope.

The combination of pentoxifylline and vitamin E has been utilized to ameliorate RF. Pentoxifylline inhibits fibroblast proliferation and extracellular matrix production and increases collagenase activity [35]. Vitamin E is an antioxidant that inhibits platelet aggregation, collagen, and TGF-β. Pentoxifylline together with vitamin E were found to improve tissue compliance following breast radiation [36]. A pilot study for radiation-induced trismus found improvement in mouth opening and fibrosis with pentoxifylline [37]. However, this combination usually requires long treatment (mean of 2 years), and there is a risk of a rebound effect if treatment is too short [38]. This study recommended treatment for 3 years or more for those with severe RF. A recent study found that compliance with pentoxifylline and vitamin E is

Table 1 Agents and targets studied for radiation fibrosis

Molecule/medication	Target	Site	Reference(s)
Thalidomide	TGF-β1, Smad3	Lung Kidney Heart	Bian et al. 2018 [23] Scharpfenecker et al. 2014 [56] Hoving et al. 2013 [24]
Galunisertib	TGF-β receptor 1	Lung	Dadrich et al. 2016 [30]
LY2109761	TGF-β receptor 1	Lung Liver	Flechsig et al. 2012 [18] Luangmonkong et al. 2018 [19]
SM16	TGF-β receptor 1	Lung	Anscher et al. 2008 [57]
Halofuginone	TGF-β receptor 2	Lung Breast Soft tissue	Calik et al. 2017 [22] Xavier et al. 2004 [20] Ishii at al. 2009 [21]
Quercetin	Cofilin, TGF-β	Skin Lung	Horton et al. 2013 [58] Liu et al. 2013 [59]
siRNA	Smad3	Skin	Lee et al. 2010 [60]
6.3G9 monoclonal Ab	α5β6 Integrin	Lung	Puthawala et al. 2008 [61]
SEW2871, fTy50	SPT	Heart	Gorshkova et al. 2013 [62]
Myriocin	SPT	Lung	Gorshkova et al. 2012 [63]
MSK-122	CXCR4/CXCL12	Lung	Shu et al. 2013 [64]
Y-27632	Rho kinase	Intestine	Bourgier et al. 2005 [65]
Imatinib	PDGF tyrosine kinase	Ovary Lung Skin Lung	Asadi-Azarbaijani et al. 2019 [29] Dadrish et al. 2016 [30] Horton et al. 2013 [28] Abdollahi et al. 2005 [25]
SU9518	PDGF tyrosine kinase	Lung In vitro cells Lung	Dadrish et al. 2016 [30] Li et al. 2006 [26] Abdollahi et al. 2005 [25]
SU11657	PDGF tyrosine kinase	Lung	Abdollahi et al. 2005 [25]
Simvastatin	HMG-CoA reductase	Lung	Mathew et al. 2011 [66]
Enalapril	ACE	Lung	Gao et al. 2013 [67]
Bone marrow-derived mesenchymal cells	Inflammation	Skin Lung	Horton et al. 2013 [68] Klein et al.2017 [69]
Amifostine	ROS	Bone marrow/intestine/lung Heart Lung/skin	Cheema et al. 2019 [70] Gurses et at. 2018 [71] Koukourakis et al. 2013 [72]
SOD-TAT	ROS	Lung	Pan et al. 2012 [73]
Pirfenidone	Multiple targets -Inhibition of TGF-β, TNF, IL-10, p38α and p38γ, and p38α	Lung Intestine Lung	Hang et al. 2020 [33] Sun et al. 2018 [31] Qin et al. 2018 [32] Simone et al. 2007 [34]
Pentoxifylline and vitamin E	Human dermal fibroblast proliferation, extracellular matrix production, collagenase activity Antioxidant	Breast ROM and lymphedema Skin Lymphedema Trismus	Jacobson et al 2013 [36] Magnusson et el. 2009 [41] Delanian et al. 2003 [38] Gothard et el. 2004 [40] Chua et el.2001 [37]
Collagenase of the bacterium *Clostridium histolyticum*	Collagen molecules	Capsular contracture model	Diehm et al. 2019 [45]
Botulinum toxins	SNARE complex	Salivary glands Salivary glands	Zeidan et al. 2016 [54] Teymoortash et al 2009 [55]

worse in clinical practice than published studies suggest, with nausea cited as the most common reason for cessation [39•]. Although several studies have shown amelioration of RF [36–38], other studies have not found a benefit [40, 41]. This may be related to endpoints utilized in studies, as Magnusson et al. showed a significant difference in arm volume but no significant difference in abduction range of motion, Visual Analogue Scale, or the total score for the Late Effects on Normal Tissue (Subjective, Objective, Management and Analytic).

Interventional procedures with botulinum toxins and collagenase clostridium histolyticum are being investigated for their role in mitigating RF and its sequelae. Collagenase clostridium histolyticum is a metalloprotease that cleaves the collagen triple helix. Injections with this collagenase have been utilized in the treatment of conditions with fibrotic process such as Dupuytren contractures [42], Peyronie disease [43], and plantar fibromatosis [44]. More recently collagenase clostridium histolyticum was studied in the treatment of irradiation-induced capsular contracture in rat models and found to be successful in degrading irradiation-induced capsular fibrosis around silicone implants [45]. Although distinct from RF, it has also been hypothesized that it may help ameliorate spastic muscle contracture for children with cerebral palsy [46] suggesting at the potential for further applications in the setting of RF.

Botulinum toxin injections have been utilized in the management of sequalae of RFS including cervical dystonia and trismus [47]. This use has been investigated by several studies with small (N=6–19) sample sizes [48–50]. Additionally, it has been found to beneficial for individuals with keloid scars [51] and in models of fibrotic skin conditions including hypertrophic scars [52] and skin fibrosis in systemic sclerosis [53]. More specific to late effects of RF, botulinum toxin injections were also found to attenuate radiation-induced saliva dysfunction in mice [54] and rats [55].

Treatment Paradigms

Unfortunately, at this time, there is no cure for RFS. This article highlights several biologic and molecular targets being investigated to ameliorate RF. These novel endeavors bring hope for potential pharmacologic interventions in the future, but at this time, most are in preclinical stages, and several have mixed results. Of the few agents studied in humans, pirfenidone was investigated in a small pilot study and is already FDA approved for idiopathic pulmonary fibrosis. Pentoxifylline and vitamin have mixed results in human studies and require a long treatment course. Botulinum toxin injections are being utilized to address cervical dystonia and trismus from RFS, and collagenase is under investigation in capsular contracture models. Additional exploration of these targets is needed to better understand dosing, safety, and implementation. As we await additional data, treatment continues to be centered on addressing symptoms and improving and maintaining function.

With early identification and treatment, there can be a meaningful impact to optimize function and quality of life while abating function impairments. Patients may present to physiatrists with decreased range of motion, pain, weakness, postural abnormalities, and numerous other musculoskeletal functional impairments. Management includes patient education, therapy interventions, lifelong home exercise, orthotics, assistive devices, pain control, injection procedures, and pharmacotherapy. Given the progressive nature of RFS, the primary treatment goal is to enhance and maintain function in the setting of anticipated progression of symptoms. Additionally, there are unique neuro-musculoskeletal sequelae such as myelo-radiculo-plexo-neuro-myopathy, cervical dystonia, trismus, and dropped head syndrome that benefit from specialized and comprehensive cancer rehabilitation treatment [4].

Myelo-radiculo-plexo-neuro-myopathy describes the presentation of RF impacting anywhere along neuro-muscular structures such as is seen in dropped head syndrome. Dropped head syndrome refers to atrophy and weakness of the cervicothoracic and shoulder girdle muscles [74, 75]. The cornerstone of treatment is physical therapy and a lifelong home exercise program focused on postural retraining, strengthening of cervicothoracic and rotator cuff muscles, core strengthening, and range of motion [4]. Additionally, myofascial release can improve pain, function, range of motion, and posture [76]. If head positioning is not able to be maintained, cervical collars [77] can be considered; however, patient may not enjoy using them. Ideally a cervical collar would only be used as needed for energy conservation, while continuing to participate in a home exercise program to work towards optimizing strength, range of motion, and posture [4, 77].

Cervical dystonia is another clinical manifestation that comprised painful dystonic spasms of cervical muscles including the sternocleidomastoid, scalenes, and trapezius [78]. In addition to major impacts on neck function, cervical dystonia can also affect swallowing, speech, and the ability to perform activities of daily living [4]. Similarly, mainstays of treatment are physical therapy and lifelong home exercise programs as above. To address neuropathic pain, pharmacotherapy options include gabapentin, pregabalin, and duloxetine [78]. Botulinum toxin injections can also be considered and can help decrease pain; however, these should be performed in conjunction with therapy to help address range of motion [47, 48].

Trismus, or the limited ability to open the mouth, is another potential manifestation of RF. This has been shown to negatively impact eating, oral hygiene, quality of life, anxiety, and

depression [79]. Physical therapy and a home exercise program to treat trismus include active range of motion, hold/relax techniques, manual stretching, and joint distraction [80]. Jaw stretching devices such as the TheraBite® Jaw Motion Rehabilitation System™ and the Dynasplint® Trismus System can help improve range of motion [81, 82]. Botulinum toxin injections for trismus were also found to decrease pain but did not improve jaw opening [49].

Rehabilitation Implications

RFS yields many challenges for the treating physiatrist, both from clinical and research perspectives. As summarized above, there are only a handful of therapeutics currently available to clinicians to treat or slow the progression of RF. Interventional procedures such as chemodenervation also have shown mixed results with regard to effectiveness in improving functional outcomes and range of motion in those with RF. As such, emphasis of a lifelong home exercise program is critical to preserving range of motion and reducing the risk for limb dysfunction following radiation treatments. The benefit of having a physiatrist familiar with the peripheral nervous system to provide early detection and intervention for lymphedema, skin breakdown, and myelo-radiculo-plexo-neuro-myopathies related to prior radiation treatments is of paramount importance.

From the research standpoint, further elucidation of molecular pathways to provide more targets for development of therapeutics as well as therapeutics targeted at established molecular pathways are needed. Additionally, clinical trials focused on validating more objective grading systems to measure the degree of RF of the soft tissues are also crucial. Without an objective grading system to adequately monitor and quantify the amount of fibrosis present in the soft tissues, it will be difficult to reliably detect changes in tissue composition beyond gross functional assessments, subjective grading scales, and range of motion measurements. Sensitive, objective imaging modalities that could be developed as a means of grading the degree of fibrosis would go a long way towards ensuring that patients with RFS are detected early and managed appropriately with hopefully minimal treatment side effects or adverse impacts on their overall function.

Conclusion

RF is progressive, pathologic tissue sclerosis that occurs following radiation therapy. The clinical presentation of RFS varies depending on the tissues involved. Noteworthy neuromusculoskeletal implications for the physiatrist include cervical dystonia, trismus, dropped head syndrome, shoulder dysfunction, and myelo-radiculo-plexo-neuro-myopathy. The symptomatology of RF may present months to years following radiation therapy and progresses with time. The pathophysiology of RF is complex and involves multiple molecular pathways. The pathways involved include the ROS, DDR, TGF-β, FMP, and ICC pathways. Numerous targets are under investigation for the potential to prevent and treat RF. Agents tactically targeting TGF-β, including LY2109761, halofuginone, thalidomide, quercetin, and siRNA, have evidence of preclinical improvements in RF; however, some agents had mixed results when studied on various tissues. SU9518, SU1167, and imatinib which target PDGF have also shown preclinical improvements in RF but again with mixed results on different tissue types. In a small pilot study, pirfenidone, an antifibrotic agent, demonstrated an improvement in range of motion and subjective symptoms. Pentoxifylline together with vitamin E has been utilized in clinical practice, and with long-term use, there is some evidence of amelioration of RF; however, this too has a mixed body of evidence.

As there continues to be no cure for RF, treatment is rooted in improving and maintaining function and quality of life while minimizing symptom burden. The cornerstone of management is a lifelong home exercise program given the progressive nature of RF. This will also involve patient education and therapy interventions. Further management may include orthotics, assistive devices, injection procedures, and pharmacotherapy as indicated depending on the clinical presentation and patient goals. Given the wide breadth of novel biologic and molecular targets currently under investigation, there is good reason for optimism for the development of pharmacologic options to prevent and alleviate RF. However, at this time, most of these agents remain in preclinical trials and lack clear, consistent evidence of benefit. Additional investigation into the dosing, timing, safety, and objective grading systems is needed. Comprehensive cancer rehabilitation is imperative to identify and mitigate the clinical manifestations of RFS while optimizing function and quality of life.

Declarations

Conflict of Interest The authors do not have any potential conflicts of interest to disclose.

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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- •• Of major importance

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