Role of Pentoxifylline and Vitamin E in Attenuation of Radiation-Induced Fibrosis

Teresa B Chiao and Audrey J Lee

OBJECTIVE: To evaluate the use of pentoxifylline and vitamin E as monotherapy and in combination for the treatment of radiation-induced fibrosis (RIF).

DATA SOURCES: Literature retrieval was performed through MEDLINE (1966–March 2004) using the terms vitamin E, α-tocopherol, pentoxifylline, radiation-induced fibrosis, and radiation injury.

DATA SYNTHESIS: Few treatments exist for managing RIF of soft tissues. Due to its antioxidant properties, vitamin E may reduce the oxidative damage induced by radiation. The precise mechanism of action for pentoxifylline in management of RIF remains unclear. Uncontrolled studies evaluating vitamin E or pentoxifylline as monotherapy in RIF have shown modest improvement in clinical regression of fibrosis. However, controlled data are needed to verify these benefits. Studies involving pentoxifylline plus vitamin E demonstrated regression in RIF. The combination was more effective than placebo and may be superior to monotherapy with either agent. Adverse effects were rarely reported in the studies and consisted mainly of gastrointestinal and nervous system effects.

CONCLUSIONS: Overall, pentoxifylline is well tolerated and is one of the few commercially available drugs with clinical data for management of RIF. Despite a lack of large, well-designed clinical trials, pentoxifylline plus vitamin E should be considered as an option in patients with symptomatic RIF.

KEY WORDS: α-tocopherol, pentoxifylline, radiation-induced fibrosis, vitamin E.

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REQUEST

Is pentoxifylline plus vitamin E effective for treatment of radiation-induced fibrosis (RIF)?

RESPONSE

Background

Late or chronic fibrosis of soft tissues represents a serious and common complication of radiation therapy in the treatment of malignancy.[1,2] Few treatment modalities exist for managing RIF.[2] Pentoxifylline, a methylxanthine derivative approved by the Food and Drug Administration for the treatment of patients with intermittent claudication, is one of the first medications available in the US that may be used to treat RIF, particularly when given in combination with vitamin E.[2-4] The literature evaluating the use of pentoxifylline and vitamin E for RIF is reviewed here.

Late radiation injuries usually do not become clinically apparent until several months or years following the completion of radiation therapy and are characterized by a loss of elasticity and mild induration.[1,2] Fibrosis can occur with more severe injury and is commonly seen in breast, head, neck, and connective tissues.[2,4-6] Complications of fibrosis include chronic pain, neuropathy, loss of joint range of motion, and lymphedema.[1] In addition to fibrosis, other late manifestations of radiation-induced injury include ulceration and necrosis associated with diminished vascular supply.[1,2,5]

The underlying mechanisms behind the development of RIF remain unknown.[2] Early theories proposed that RIF was caused by direct microvascular destruction, resulting in tissue hypoxia and nutritional deficits related to vascular insufficiency. More recent theories have implicated the role of cytokines and growth factors in the development of

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RIF. Transforming growth factor-B (TGF-B) may play a major pathologic role in RIF by stimulating recruitment and proliferation of fibroblasts, increasing fibroblast synthesis of extracellular matrix proteins (eg, collagen), and decreasing breakdown of extracellular matrix.[2,6-8] Cytokines such as tumor necrosis factor (TNF) and interleukin-1 may play a fibrogenic role by stimulating inflammation, cell migration, and proliferation.[2,6,7]

The onset of RIF has been reported to occur from 4–6 months to 1–2 years following exposure to radiation therapy[1,5] and progresses in severity over time.[2,5] Significant risk factors for RIF include high total radiation dose (>63 Gy) and large dose per fraction (≥1.8 Gy).[1,5] Additional risk factors include large volumes of tissue exposed to radiation and radiotherapy combined with surgery, chemotherapy, or both.[2,5,9]

A rating scale commonly used to evaluate RIF in clinical trials is the SOMA (subjective, objective, management, analytic) scale.[1] The SOMA scale evaluates 14 items, such as fibrosis and other types of late tissue injuries (eg, ulcers, edema), based upon a 5-point scale.[1,10] According to this scale, 1 = minor symptoms requiring no treatment, 2 = moderate symptoms requiring conservative treatment, 3 = severe symptoms that interfere with daily activities and require more aggressive treatment, 4 = irreversible damage requiring major treatment, and 5 = death or loss of an organ.[10] The SOMA score has been reported in the literature as an item average (total score/14) or total score.[2,11,12]

Treatment for RIF

Few treatments exist for managing RIF of soft tissues.[2,4] Although physiotherapy will not prevent or reverse the late effects of radiation therapy, limited controlled data suggest that it may help improve the range of motion of patients and is frequently considered standard of care.[2] Microcurrent therapy may also play an adjunctive role.[2,13,14] Well-designed trials are still needed to validate the benefits of these treatment modalities.

Data documenting the benefits of pharmacologic therapy are also limited.[2,4] Clinical and experimental data suggest that superoxide dismutase, an anti-oxidant agent, reduces skin or soft tissue RIF; however, it is an investigational agent.[2,4,15-17] Of the commercially available agents, in vivo and in vitro studies demonstrated that interferon gamma-1b and interferon alfa-2b decrease collagen synthesis[2]; however, only 3 small, uncontrolled studies support their clinical use.[2,9,18] Other limitations of the interferons are that they are available only as injections and can be associated with significant toxicity.[19]

Vitamin E

It has been proposed that vitamin E (eg, α-tocopherol) may have therapeutic benefits in combating RIF due to its antioxidant properties and its inhibition of TGF-B and collagen production.[2,12,20] The outcomes of 53 consecutive patients with breast cancer who developed RIF treated with vitamin E have been reported (Table 1).[21] Vitamin E reduced the average fibrosis by 20%. Overall, 34 patients had diminished fibrosis and 4 patients had complete resolution. Among the 38 patients whose fibrosis diminished or disappeared, nearly half redeveloped fibrosis. Improvement in the dimensions of fibrosis (not defined) was observed in 55% of patients during the observation period (3–82 mo).

A clinical trial randomized patients with breast cancer who developed RIF to various treatment groups, including vitamin E plus placebo (n = 6) and double placebo (n = 6) (Table 1).[12] There appeared to be no difference between these groups in mean RIF surface area or volume regression or SOMA score at 6 months, although statistics were not reported.

Pentoxifylline Monotherapy

Several mechanisms of action have been proposed for the potential benefits of pentoxifylline in the management of RIF; however, the precise mechanism remains unclear.[2] Pentoxifylline may decrease fibrosis by reducing blood viscosity and improving erythrocyte flexibility, leading to increased blood flow and higher tissue oxygenation.[2-4] Pentoxifylline may also decrease the inflammatory response and formation of oxygen radicals induced by radiation injury by inhibiting neutrophil activity and adhesion.[2,3] Pentoxifylline has also been shown to decrease fibroblast, cellular matrix, and collagen production by blocking the activity of TNF, decreasing production of interleukin (eg, 1-B), and stimulating collagenase activity.[12,20,22]

Studies have reported that pentoxifylline either prevents or induces regression of RIF,[20,23] and a case report demonstrated symptomatic improvement after pentoxifylline therapy (Table 1).[24] In addition, an uncontrolled trial involving 12 patients with radiation necrosis of soft tissue demonstrated that pentoxifylline 400 mg administered orally 3 times a day for 6 months resulted in complete healing at 87% (13 of 15) of the necrotic sites.[25] These results prompted the investigation of pentoxifylline as monotherapy for late radiation injuries in 3 studies.[12,26,27]

The first uncontrolled trial evaluated at least 3 months of pentoxifylline therapy in 26 patients with head and neck cancer who experienced late radiation injuries (necrosis, fibrosis, mucosal pain) that had not responded after 8 weeks of treatment with oral antibiotics, analgesics, superficial debridement, and local wound care.[26] For patients in whom a complete response occurred (100% healing = complete epithelialization), pentoxifylline was continued for an additional month. Among 15 patients with soft-tissue necrosis, 9 had complete healing and 3 had >75% reduction in ulcer size (average time to healing: onset of response 7.2 wk, maximum response 17 wk). Of 6 patients with fibrosis, 2 had no measurable response. The remaining 4 patients had an improved clinical response while on therapy (average time to healing: onset of response 12 wk, maximum response 13 wk). One patient had >50% improvement in range of motion and a 90% reduction in induration. Two patients had a 50% reduction in induration and fibrosis and 1 had a 20% reduction. All patients with fibrosis who responded had marked pain relief. Four of 5 pa-

Table 1. Clinical Trials

Reference	Design	Pts.	Age (y)	Radiation Dose	Treatment	Results
Vitamin E monotherapy						
Baillet (1997)[21]	retrospective, OL, uncontrolled	N = 53, RIF following radiation therapy for breast cancer	NR	NR	vitamin E (α-tocopherol) 700 mg/day po average (range 500–1500) for 3.5 mo	average diameter of RIF ↓ from 6.8 to 5.4 cm (20% reduction) RIF ↓ in 64% and disappeared in 8% RIF recurred in 47% of pts. who initially had a response
Delanian et al. (2003)[12,a]	R, DB, PC	N = 22 women, RIF following radiation therapy for breast cancer	average 57	NR	vitamin E[b] 1000 units/day po (500-unit capsules) + placebo po (n = 6); double placebo (n = 6) for 6 mo	at 6 mo: mean RIF surface area regression: vitamin E + placebo (40.0%), double placebo (42.6%)[c] mean RIF volume regression: vitamin E + placebo (52.8%), double placebo (50.8%)[c] mean SOMA score: vitamin E + placebo (7.0; 37.1% reduction), double placebo (7.4; 32.9% reduction)[c]
Pentoxifylline monotherapy						
Werner-Wasik (1993)[24]	case report	female with RIF following excision and radiation therapy for breast cancer	56	45–66.4 Gy	PTX[b] 400 mg po tid for 6 wk	pain and tenderness improved by 3 wk and resolved by 6 wk; she remained asymptomatic for an additional 6 wk
Futran et al. (1997)[26]	prospective, OL, uncontrolled	n = 15, soft-tissue necrosis n = 6 pts., RIF n = 5 pts. with mucosal pain	average 62.4	NR	controlled-release PTX 400 mg po q8h for 3 mo	response in 12/15, 4/6, 5/5, respectively
Cornelison et al. (1996)[27]	OL, uncontrolled	N = 8, RIF of the neck, chest wall, pelvis, or extremities	15–72	40–68 Gy	PTX[b] 400 mg po tid for 8 wk	all 8 pts. met improvement criteria: 8/8 had improved active ROM 6/8 had improved passive ROM 3/7 had decreased pain 5/8 had improved motor strength 3/7 had increased tissue compliance
Delanian et al. (2003)[12,a]	(see above)	(see above)	(see above)	(see above)	PTX[b] 800 mg/day po (400-mg tablets) + placebo po (n = 5); double placebo (n = 6) for 6 mo	at 6 mo: mean RIF surface area regression: PTX + placebo (39.1%), double placebo (42.6%)[c] mean RIF volume regression: PTX + placebo (48.6%), double placebo (50.8%)[c] mean SOMA score: PTX + placebo (7.6; 32.4% reduction), double placebo (7.4; 33% reduction)[c]

CT = computed tomography; DB = double-blind; MRI = magnetic resonance imaging; NR = not reported; OL = open-label; PC = placebo-controlled; PTX = pentoxifylline; R = randomized; RIF = radiation-induced fibrosis; ROM = range of motion; SOMA = subjective, objective, management, analytic.

[a]Used ultrasonography to measure depth of RIF.

[b]Formulation not specified.

[c]p Value NR.

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Table 1. Clinical Trials (continued)

Reference	Design	Pts.	Age (y)	Radiation Dose	Treatment	Results
Pentoxifylline plus vitamin E						
Delanian (1998)[28]	case report	female with cervical thoracic RIF following surgery, chemotherapy, concomitant radiation therapy for small-cell thyroid carcinoma	67	50 Gy total	PTX[b] 800 mg/day po +vitamin E[b] 1000 units/day po for 18 mo	linear dimensions regressed from 10 × 8 cm at 3 mo to unmeasurable at 18 mo SOMA scale decreased from 15 at 3 mo to 1 at 18 mo cervical rotation normalized local inflammatory signs resolved CT scan at 18 mo showed complete disappearance of fibrosis
Fischer et al. (2001)[29,a]	case report	female with ulcerated RIF following surgery and radiation therapy for breast cancer	60	40 Gy total	PTX[b] 400 mg po tid + vitamin E[b] 400 mg/day po (duration NR)	decreased pain at 12 wk ulcers healed by 18 mo dermal thickness decreased from 5.6 to 2.6 mm at 12 mo
Delanian et al. (2002)[30]	case report	female with osteo-radio-necrosis and breast fibrosis following surgery and radiation therapy for breast cancer	68	NR	PTX[b] 800 mg/day po + vitamin E (α-tocopherol) 1000 IU/day po for at least 3 y	inflammation decreased at 3 mo fibrotic area regressed from 15 × 11 cm to 9 × 7 cm at 12 mo MRI showed total regression of clinical fibrosis after 3 y
Delanian et al. (1999)[11]	prospective, OL, uncontrolled	N = 43, 50 zones of RIF refractory to prior treatments including cortico-steroids	average 59	7 pts.: 1.8–2.5 Gy per fraction; total 45–75 Gy; (dose to an area may have exceeded 90 Gy due to treatments to adjacent overlapping areas)	PTX[b] 400 mg po + vitamin E[b] 500 IU po bid for at least 6 mo	mean 53% regression of RIF surface area ($p < 0.0001$) mean dimension ↓ from 6.5 to 4.5 cm objective response (>50% RIF surface regression) in 60% at 6 mo and 83% at 12 mo mean SOMA score ↓ from 13.2 to 6.9 23 of 24 pts. no longer required analgesics
Delanian et al. (2003)[12,a]	(see above)	(see above)	(see above)	(see above)	PTX[b] 800 mg/day po (400-mg tablets) + vitamin E[b] 1000 units/day po (500-unit capsules) (n = 5); PTX[b] + placebo (n = 5); placebo + vitamin E[b] (n = 6); double placebo (n = 6) for 6 mo	mean RIF surface area regression: PTX + vitamin E (60.2%), PTX + placebo (39.1%), vitamin E + placebo (40.0%), double placebo (42.6%); p = 0.038 for PTX + vitamin E vs double placebo mean RIF volume regression: PTX + vitamin E (73.0%), PTX + placebo (48.6%), vitamin E + placebo (52.8%), double placebo (50.8%); p = 0.054 for PTX + vitamin E vs double placebo mean SOMA score: PTX + vitamin E (7.0; 39.1% reduction), PTX + placebo (7.6; 32.4% reduction), vitamin E + placebo (6.0; 37.1% reduction), double placebo (7.4; 32.9% reduction)[c]

CT = computed tomography; DB = double-blind; MRI = magnetic resonance imaging; NR = not reported; OL = open-label; PC = placebo-controlled; PTX = pentoxifylline; R = randomized; RIF = radiation-induced fibrosis; ROM = range of motion; SOMA = subjective, objective, management, analytic.
[a]Used ultrasonography to measure depth of RIF.
[b]Formulation not specified.
[c]p Value NR.

tients with mucosal pain had complete resolution of their pain, while one had improvement (average time to healing: onset of response 4.3 wk, maximum response 8.7 wk).

The second uncontrolled study evaluated 8 weeks of pentoxifylline therapy in 8 patients with RIF All patients improved in active range of motion. Three of 7 patients had decreased pain and one ceased narcotic use. At a 16-week follow-up, 4 patients had sustained improvement (not defined).

The third study randomized patients with breast cancer who developed RIF to various treatment groups, including pentoxifylline plus placebo (n = 5) and double placebo (n = 6).[12] In contrast to the uncontrolled trials, there appeared to be no difference between these groups in mean RIF surface area, mean volume regression, or SOMA score at 6 months.

Pentoxifylline plus Vitamin E

Case reports of pentoxifylline plus vitamin E in patients with RIF have demonstrated clinical regression of fibrosis and improvement in clinical symptoms (eg, skin tightness, dyspnea, pain; Table 1).[28-30] Due to the positive results from these reports, 2 studies evaluated the use of pentoxifylline plus vitamin E in patients with RIF (Table 1).[11,12]

An uncontrolled trial evaluated at least 6 months of therapy with pentoxifylline plus vitamin E in patients with 50 distinct areas of RIF refractory to prior treatments.[11] Nine patients had limited arm, leg, or neck range of motion related to RIF, 6 had nerve dysfunction, 12 had local inflammation, and 8 had severe edema. Forty-one of the RIF areas were caused by adjuvant postoperative radiotherapy for breast cancer. Response was classified according to percent of RIF surface area regression at 6 months, with no response (0–24%) occurring in 2 areas, slight response (25–49%) in 14 areas, moderate response (50–74%) in 18 areas, and excellent response (75–100%) in 6 areas. Complete response occurred in 3 areas. There was a mean 53% regression of the RIF surface area at 6 months ($p < 0.0001$). The percentage of patients who achieved objective responses (>50% RIF surface regression) increased over the course of the study, reaching 83% at 12 months, whereas the mean SOMA score improved from 13.2 at baseline to 6.9. Twenty-three of the 24 patients who required analgesics at baseline discontinued these medications. Of 12 RIF areas with inflammation at baseline, no local inflammatory signs were present after 12 months.

Two patients with necrosis at baseline had superficial improvement after 3 months of treatment; however, no results were reported at 12 months. Furthermore, patients with limited range of shoulder and neck movement at baseline experienced improvement in rotational movement. Although there was no improvement of neurologic function at 6 months, nerve dysfunction had not progressed in severity, while at 12 months neurologic function improved in only one case. The frequency of reported episodes of edema decreased from every month to every 3 months after 6 months of therapy. Overall, this uncontrolled trial suggested that pentoxifylline plus vitamin E improved subjective and objective findings of RIF.[11]

To further test the theoretical benefit of pentoxifylline and vitamin E in RIF, Delanian et al.[12] conducted a clinical trial in patients with breast cancer who developed RIF (N = 22).[12] Patients were randomized to receive 6 months of therapy with one of 4 treatments: pentoxifylline plus vitamin E, pentoxifylline plus placebo, placebo plus vitamin E, or double placebo. The size of the fibrotic surface area was measured by palpation of the edges and measurement of the projected cutaneous surface. Ultrasonography was utilized to measure the depth of the fibrotic tissue. At 6 months, pentoxifylline plus vitamin E significantly reduced fibrotic surface area ($p = 0.038$) and volume ($p = 0.054$) compared with double placebo and appeared to be more effective than monotherapy with either agent (p value NR). Pentoxifylline plus vitamin E demonstrated significantly faster surface area ($p = 0.018$) and volume regression ($p = 0.025$) on slope analysis compared with double placebo. In addition, pentoxifylline plus vitamin E showed significantly faster volume regression on slope analysis compared with all other treatment groups ($p = 0.036$). The mean change in SOMA score at 6 months did not appear to be different among treatment groups (p values NR).

Study Limitations

Each study was limited by its small sample size and heterogeneous patient population (eg, location of fibrosis and radiation treatments). In addition, dosing regimens for pentoxifylline and vitamin E were dissimilar among studies. None of the studies evaluated patient adherence and only one was blinded. Non-pharmacologic therapy and pain management were not specified in any of the studies, and some did not evaluate patients for risk factors for fibrosis such as radiation dose. The majority of measures used to evaluate efficacy were also based on subjective assessments, and the types of efficacy measures varied across the studies.

Adverse Effects

Adverse effects that commonly occur with pentoxifylline when used for intermittent claudication include dose-related gastrointestinal and central nervous system effects.[3] Similar adverse effects were reported in studies evaluating pentoxifylline for RIF. Cornelison et al.[27] reported adverse effects that included mild and severe nausea, dyspepsia, jitteriness, and insomnia with pentoxifylline. In a randomized, placebo-controlled trial, 10 (45%) patients experienced adverse effects, but there was no difference in the incidence among the treatment groups.[12] Adverse effects included nausea, hot flashes, asthenia, headache, epigastralgia, and vertigo, but none led to discontinuation of therapy. In an uncontrolled trial, 2 patients experienced mild gastrointestinal effects.[11] Another 2 patients in this trial experienced nervous system adverse effects (asthenia, vertigo) after 3 months of therapy, requiring discontinuation.

Summary

Overall, pentoxifylline is well tolerated and is one of the few commercially available drugs with clinical data for

management of RIF. Uncontrolled studies in which vitamin E or pentoxifylline monotherapy was evaluated in RIF have shown modest improvement in clinical symptoms and regression of fibrosis. In contrast, one small, controlled trial appeared to show no benefit with pentoxifylline or vitamin E monotherapy. Larger controlled trials are needed to establish the benefits of either agent for RIF. Studies evaluating combination therapy have demonstrated that pentoxifylline plus vitamin E significantly reduces RIF by 6 months and appears to be superior to monotherapy with either vitamin E or pentoxifylline. However, large randomized, blinded, controlled trials are needed to substantiate these findings and to determine the optimum doses for pentoxifylline and vitamin E.

Despite a lack of consistent findings or evidence from multiple, well-designed, randomized controlled studies, pentoxifylline plus vitamin E should be considered as a treatment option in patients with symptomatic RIF due to ease of administration, favorable safety profile, and limited treatment options. Although the optimum dose and duration of pentoxifylline plus vitamin E therapy need to be established, clinicians can initiate pentoxifylline 400 mg orally twice per day (up to 1200 mg/day) plus vitamin E 1000 IU orally daily based on available data.

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EXTRACTO

OBJETIVO: Evaluar el uso de pentoxifilina y vitamina E como monoterapia y en combinación en el tratamiento de fibrosis inducida por radiación (FIR).

FUENTES DE INFORMACIÓN: Se realizó una búsqueda de literatura a través de MEDLINE (1966–marzo 2004) utilizando los términos vitamina E,

alfa tocoferol, pentoxifiline, fibrosis inducida por radiación, y daño por radiación.

SÍNTESIS: Existen pocos tratamientos para el manejo de FIR de tejido blando. Por sus propiedades antioxidantes, la vitamina E podría reducir el daño oxidativo inducido por radiación. El mecanismo de acción exacto de pentoxifilina en el manejo de FIR aun no se ha definido. Estudios no controlados que han evaluado el uso de vitamina E o pentoxifilina como monoterapia en FIR han demostrado una leve mejoría en la regresión clínica de la fibrosis. Sin embargo, se necesitan estudios controlados que confirmen estos beneficios. Estudios que han utilizado pentoxifilina y vitamina E han demostrado regresión en FIR. La combinación fue más efectiva que placebo y podría ser superior a monoterapia con cualquiera de los agentes. Los efectos adversos fueron reportados raramente en los estudios y consistieron mayormente de efectos gastrointestinales y del sistema nervioso.

CONCLUSIONES: En general, pentoxifilina es bien tolerado y es uno de los pocos medicamentos disponibles comercialmente con evidencia clínica para el tratamiento de FIR. Aunque no existen estudios clínicos bien diseñados y con un número extenso de pacientes, pentoxifilina y vitamina E deben ser considerados como una alternativa en pacientes con FIR sintomático.

Annette Pérez

RÉSUMÉ

OBJECTIF: Evaluer la pentoxyfilline et la vitamine E en monothérapie et en association dans le traitement de la fibrose radio-induite (FRI).

REVUE DE LITTÉRATURE: Littérature repérée par une recherche sur MEDLINE (1966 à mars 2004); mots-clés: vitamine E, α-tocophérol, pentoxyfilline, fibrose radio-induite, et dommages radiatifs.

RÉSUMÉ: Il y a peu de traitements pour la prise en charge de la FRI des tissus mous. En raison de ses propriétés antioxydantes, la vitamine E est susceptible de réduire les dommages oxydants radio-induits. Le mécanisme d'action précis de la pentoxyfilline dans la prise en charge de la FRI reste à élucider. Des études non contrôlées évaluant la vitamine E ou la pentoxyfilline en monothérapie dans la FRI ont montré une amélioration modeste en termes de régression clinique de la fibrose. Néanmoins, des données contrôlées sont nécessaires pour vérifier ces bénéfices. Les études évaluant la pentoxyfilline associée à la vitamine E ont montré une régression de la FRI. L'association a été plus efficace que le placebo et serait supérieure à la monothérapie par chacun des produits. Des effets indésirables ont rarement été rapportés dans ces études; ils concernaient surtout la sphère gastro-intestinale et le système nerveux central.

CONCLUSIONS: Dans l'ensemble, la pentoxyfilline est bien tolérée et est un des rares médicaments disponibles avec des données sur la prise en charge de la FRI. Malgré l'absence d'essais bien conduits et de forts effectifs, l'association de pentoxyfilline et de vitamine E devrait être envisagée comme une possibilité chez des patients avec une FRI symptomatique.

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