Management of acute radiation dermatitis: A review of the literature and proposal for treatment algorithm

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Radiation dermatitis is a common sequela of radiation therapy; up to 95% of patients will develop moderate-to-severe skin reactions. No criterion standard currently exists for the treatment of acute radiation-induced skin toxicity. It is therefore imperative to develop a greater understanding of management options available to allow clinicians to make informed decisions when managing radiation oncology patients. This literature review discusses the topical agents that have been studied for the treatment of acute radiation dermatitis, reviews their mechanisms of action, and presents a treatment algorithm for clinicians managing patients experiencing radiation dermatitis. (J Am Acad Dermatol 2019;81:558-67.)

Key words: aloe vera; ascorbic acid; β-sitosterol; calendula; catechins; chamomile; corticosteroids; dermatitis; epidermal growth factor; granulocyte macrophage-colony stimulating factor; hyaluronic acid; management; pantothenic acid; prevention; radiation; radiation dermatitis; radiation-induced skin toxicity; radiation oncology; radiotherapy; silver clear nylon dressing; silver sulfadiazine; statins; steroids; sucralfate; topical; topical agents; treatment; trolamine; washing.

Radiation dermatitis (RD) is a common sequela of radiation therapy (RT). Up to 85% of patients treated with RT develop moderate-to-severe skin reactions.[1,2] These adverse cutaneous effects encompass characteristic skin changes, including edema, erythema, dyspigmentation, and necrosis. The Radiation Therapy Oncology Group (RTOG) has developed a standardized grading system to evaluate acute radiation-induced skin toxicity (Table I).[3]

Toxicity from RT is complex and secondary to a variety of factors, such as total radiation dose, dose fractionation schedule, and volume of organ or tissue treated, as well as concurrent chemotherapy and comorbid conditions.[4] RT exhibits biologic effects within hours to weeks of exposure, causing extensive genetic damage that irreversibly breaks double strands in nuclear and mitochondrial DNA and inhibits cells' ability to divide and replicate. This damage, along with other structural tissue destruction, generation of reactive oxygen species (ROSs), a decrease in functional stem cells, initiation of epidermal and dermal inflammatory responses, and skin cell necrosis, results in RD.[5]

RD significantly affects affected patients' quality of life[6] and management of their disease.[7] No criterion standard currently exists for the treatment of acute radiation-induced skin toxicity. It is therefore imperative to develop a greater understanding of the therapeutic options available to allow clinicians to make informed decisions when managing radiation oncology patients. The objective of this literature review is to discuss the topical agents previously studied for the treatment of acute RD and emphasize those options that have proved successful in hope of guiding future clinical medicine.

HYGIENIC OPTIONS

Washing

Certain basic hygiene practices have proved beneficial in the management of radiation-induced skin toxicity. Washing with a mild soap and lukewarm water has been thoroughly studied and is currently recommended by many practicing

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clinicians.[7] Two large randomized controlled trials (RCTs) demonstrated that washing with mild soap and water, compared with no washing, results in significantly less itching and decreased RTOG dermatitis scores.[8,9]

HERBAL OPTIONS

Calendula

A member of the English marigold family, *Calendula officinalis* has been shown to have many wound-healing properties, including anti-inflammatory, antibacterial, antifungal, antioxidant, and angiogenic abilities.[10-12] These reparative properties led Pommier et al to study the role of calendula in the management of RD in a large RCT. When compared with trolamine, calendula significantly lowered the frequency of RTOG grade 2 or higher dermatitis among those assigned to treatment with calendula (41% vs 63% [$P < .001$]). Further, patients assigned to calendula treatment had fewer interruptions in RT and reported less radiation-induced pain.[13]

CAPSULE SUMMARY

- Nearly 95% of patients undergoing radiotherapy will develop radiation dermatitis; however, no criterion standard for management exists.
- Washing with mild soap and water and use of topical corticosteroids and silver nylon dressings should be recommended by clinicians for the management of acute radiation dermatitis.

Catechins

Catechins are a group of phenolic compounds that are naturally abundant in cocoa, teas, and berries. Their antioxidant activity has been shown to heal human skin damage caused by exposure to ultraviolet light.[14] Epigallocatechin-3-gallate (EGCG) is the main catechin found in green tea, and several studies have established its ability to inhibit radiation-induced damage in human skin cells and mice studies.[15-17] EGCG protects cells from ROSs through its ability to scavenge hydroxyl radicals, hydrogen peroxide, and superoxide anions.[18,19] Topical EGCG has been shown to be very effective in reducing patient-reported complaints associated with RD. A phase I and subsequent phase II clinical trial demonstrated the safety and tolerability of topical EGCG, as well as its ability to prevent occurrence of grade 3 or higher RD and significantly and persistently control itching, tenderness, pain, and burning.[20,21]

Aloe vera

Aloe vera is a natural, anti-inflammatory herbal therapy that has been reported to exhibit protection against radiation-induced skin damage. It is rich in vitamins, enzymes, minerals, sugars, lignin, saponins, salicylic acids, and amino acids, which are responsible for its healing abilities.[22] Despite these promising characteristics, aloe vera has not been shown to reduce severe RD,[23,24] and in a large RCT it was less effective in managing patient-reported symptoms than aqueous lotion was.[24]

Chamomile

Chamomile, a medicinal plant, contains levomenol, bisaboloids, chamazulene, and flavonoids, which are responsible for its anti-inflammatory, antibacterial, and spasmolytic properties[25,26] Despite these promising traits, studies have failed to demonstrate benefit of chamomile in managing RD.[27] Ferreira et al are currently conducting an RCT that should be followed for results.[28]

β-Sitosterol

β-Sitosterol, an active ingredient of beeswax and sesame oil, is an herbal formulation that is marketed as moist exposed burn ointment (MEBO) (comprising 0.25% β-sitosterol) with antibacterial, analgesic, and anti-inflammatory effects.[29] When compared with trolamine, MEBO yielded no significant difference in grades 2 or 3 dermatitis. However, the incidences of severe pruritus and local skin pain were both significantly reduced in the MEBO group ($P = .016$ and .02, respectively).[30]

TOPICAL VITAMINS

Ascorbic acid

Ascorbic acid, also known as vitamin C, possesses powerful antioxidant and free radical scavenging qualities.[31-33] These characteristics led Halperin et al to study the possible protective role of ascorbic acid in RT. The study failed to demonstrate any benefit of topical ascorbic acid for the management of RD.[34]

Pantothenic acid

Pantothenic acid (vitamin B_5), a component of coenzyme A, plays a central role in metabolism and is essential for normal skin integrity. Deficiency can lead to dermatitis, and excess amounts promote epithelial regeneration and formation. When compared with no treatment, topical dexpanthenol cream failed to show an enhanced protective effect against radiation-induced dermatitis.[35]

Abbreviations used:

EGCG: epigallocatechin-3-gallate
EGF: epidermal growth factor
GM-CSF: granulocyte-macrophage colony-stimulating factor
HA: hyaluronic acid
MEBO: moist exposed burn ointment
RCT: randomized controlled trials
RD: radiation dermatitis
ROS: reactive oxygen species
RT: radiation therapy
RTOG: Radiation Therapy Oncology Group
SSD: silver sulfadiazine

ENDOGENOUS AGENTS

HA

Hyaluronic acid (HA) is a carbohydrate polymer that is distributed ubiquitously throughout connective tissues and plays an important role in the dermal extracellular matrix.[36] A pilot study utilizing cultured fibroblasts has shown topical HA creams to be protective against ROS damage caused by radiation-induced hydrogen peroxide.[37] Human studies, however, have yielded opposing results. In 1 study, HA significantly reduced the incidence of high-grade RD.[38] In contrast, Pinnix et al found that areas treated with HA actually showed more severe dermatitis than did those treated with petroleum-based treatments.[36]

Biologic preparations

EGF. Epidermal growth factor (EGF) plays a major role in stimulating the proliferation of human epidermal stem cells, fibroblasts, and keratinocytes.[39,40] Experimental studies have demonstrated that EGF, which is released by platelets, macrophages and fibroblasts,[41] is increased in acute wounds and assists in healing through promotion of re-epithelialization.[42] Topical EGF has been shown to promote healing of diabetic foot ulcers[43] and general dermatitis.[44] Kang et al demonstrated that topical EGF leads to a decreased incidence of grade 2 or higher toxicity among patients with RT (compared with historic data).[45]

GM-CSF. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a lymphokine that promotes the chemotaxis of monocytes into tissues, thereby stimulating macrophage maturation.[46] In the presence of GM-CSF, macrophages secrete plasminogen-activating factor[47] and display increased phagocytic activity for bacteria, yeast,[48] and malignant cell lines.[49] When compared with patients treated with topical steroids alone, patients who received topical steroids with GM-CSF–soaked gauze demonstrated reduced RD scores, as well as decreased pain.[50]

Table I. Radiation Therapy Oncology Group classification for acute radiation dermatitis

Grade	Clinical presentation
Grade 0	Normal skin; no visible changes to the skin
Grade 1	Follicular, faint, or dull erythema; epilation; dry desquamation; decreased sweating. Mild tightness of skin and itching may occur. In darker skin types, the affected area may appear slightly darker
Grade 2a	Tender or bright red erythema; dry desquamation; skin may feel tight, sore and itchy. In darker skin types, the area will appear darker
Grade 2b	Patchy, moist desquamation. Yellow, pale, or green exudates may be visible on the surface. Soreness and edema are present
Grade 3	Confluent, moist desquamation other than skin folds. Yellow, pale, or green exudates will be visible on the surface. Pitting edema. Bleeding may occur
Grade 4	Ulceration and necrosis

PHARMACEUTICALS

Corticosteroids

Topical corticosteroids have anti-inflammatory effects and are often prescribed for RD because of their ability to inhibit the surge of radiation-induced cytokines.[5] Many studies have been conducted to assess the role of topical corticosteroids in both the prevention and treatment of RD. A recent 2017 meta-analysis confirmed corticosteroids' beneficial role in preventing RD. Specifically, Haruna et al found that topical corticosteroids, ranging from mild to potent, prevented the incidence of wet desquamation ($P < .0001$) and reduced the mean RD score ($P < .00001$).[51] Ho et al confirmed the efficacy of mild topical corticosteroids in decreasing moist desquamation ($P = .012$), lowering the incidence of severe skin toxicities ($P = .036$) and delaying time to development of grade 3 dermatitis ($P \leq .001$).[52] Most recently, Zenda et al have been comparing topical corticosteroids with placebo in an ongoing, multicenter trial.[53]

Statins

Statins, or 3-hydroxy-3-methyl-glutaryl–coenzyme A reductase inhibitors, are commonly prescribed for management of hypercholesterolemia and prevention of heart disease. Statins also have anti-inflammatory, immunomodulatory, antioxidant,

Table II. Summary of topical agents used in the management of RD

Topical agent	Proposed mechanism of action	Clinical efficacy	Level of evidence*
Washing	Cleansing, antimicrobial, hydrating	Proven to be useful	2
Campbell and Illingworth, 1992[8]	3-arm, randomized, controlled clinical trial (no washing vs washing with water alone vs washing with soap and water) (n = 99 patients with breast cancer)	Reduced grade of RD and patient-reported symptoms in both washing groups	
Roy et al, 2001[9]	2-arm, randomized, controlled clinical trial (no washing vs washing with mild soap and water) (n = 99 patients with breast cancer)	Reduced grade of RD and patient-reported symptoms	
Calendula	Anti-inflammatory, antibacterial, antifungal, and antioxidant properties; stimulates angiogenesis	Potentially useful	2
Pommier et al, 2004[13]	2-arm, randomized, single-blinded, controlled clinical trial (calendula vs trolamine) (n = 254 patients with breast cancer)	Reduced grade of RD and patient-reported symptoms	
Catechins	Anti-inflammatory, antibacterial, and antioxidant properties	Potentially useful	3
Zhao et al, 2015[20]	Phase I, clinical trial (topical EGCG only) (n = 24 patients with breast cancer)	Reduced grade of RD and patient-reported symptoms	
Zhu et al, 2016[21]	Phase II, clinical trial (topical EGCG only) (n = 49 patients with breast cancer)	Reduced grade of RD and patient-reported symptoms	
Aloe vera	Anti-inflammatory; rich in vitamins, enzymes, minerals, sugars, and other active constituents	Not proven to be useful	2
Williams et al, 1996[23]	2-arm, randomized, double-blind, controlled clinical trial (aloe vera vs placebo) (n = 194 patients with breast cancer)	No benefit in managing RD	
Heggie et al, 2002[24]	2-arm, phase III, randomized, double-blind, controlled clinical trial (aloe vera vs aqueous lotion) (n = 225 patients with breast cancer)	No difference in grade of RD; less effective in treating patient-reported symptoms than aqueous lotion	
Chamomile	Anti-inflammatory, spasmolytic, antibacterial	Not proven to be useful	2
Maiche et al, 1991[27]	2-arm, randomized, single-blind, controlled clinical trial (chamomile cream vs almond ointment) (n = 48 patients with breast cancer)	No benefit in managing RD	
Ferreira et al, 2016[28]	2-arm, randomized, single-blinded, controlled clinical trial (chamomile vs urea) (n = 48 patients with head and neck cancer)	Ongoing	
β-Sitosterol	Herbal formulation thought to be antibacterial with analgesic, anti-inflammatory, antiedema, and antithrombotic effects	Potentially useful	2
Geara et al, 2018[30]	2-arm, randomized, open-label study (MEBO vs trolamine) (n = 161 patients with breast cancer)	Reduced patient-reported symptoms; no difference in grade of RD	
Ascorbic acid	Antioxidant, free radical scavenging	Not proven to be useful	2
Halperin et al, 2018[34]	2-arm, randomized, double-blind, placebo-controlled clinical trial (ascorbic acid vs vehicle) (n = 84 patients with primary or metastatic brain tumors)	No benefit in managing RD	
Pantothenic acid	Antioxidant, incorporated into CoA and increases glutathione levels, promotes epithelial growth	Not proven to be useful	2
Reynolds, 1993[35]	2-arm, controlled, clinical trial (dexpanthenol cream vs no treatment) (n = 86 patients with breast and laryngeal cancer)	No benefit in managing RD	

Continued

Table II. Cont'd

Topical agent	Proposed mechanism of action	Clinical efficacy	Level of evidence*
HA	Antioxidant, involved in epidermal moisture retention	Potentially useful	2
Pinnix et al, 2012[36]	2-arm, phase III, randomized, single-blind, placebo-controlled clinical trial (topical HA vs petroleum gel) (n = 65 patients with breast cancer)	No benefit in managing RD	
Liguori et al, 1997[38]	2-arm, randomized, double-blind, placebo-controlled clinical trial (topical HA vs placebo) (n = 152 patients with head, neck, breast, and pelvic cancer)	Reduced grade of RD	
EGF	Stimulates proliferation of human fibroblasts and keratinocytes, promotes re-epithelialization	Potentially useful	4
Kang et al, 2014[45]	1-arm, multicenter prospective, open-label, observational study (EGF cream) (n = 1172 patients with various types of cancer)	Reduced grade of RD compared with in historical controls	
GM-CSF	Promotion of chemotaxis of monocytes into tissues, stimulating macrophage maturation and activation	Potentially useful	3
Kouvaris et al, 2001[50]	2-arm, prospective, clinical trial (topical steroids vs topical steroids with GM-CSF soaked gauze) (n = 61 patients with vulvar cancer)	Reduced grade of RD and patient-reported symptoms	
Corticosteroids	Anti-inflammatory; inhibits radiation-induced cytokines	Proven to be useful	1
Haruna et al, 2017[51]	Meta-analysis of 10 RCTs (n = 919 patients with breast cancer)	Reduced grade of RD	
Ho et al., 2018[52]	2-arm, randomized, double-blind, placebo-controlled, clinical trial (mometasone furoate vs Eucerin) (n = 124 patients with breast cancer)	Reduced grade of RD	
Zenda et al, 2018[53]	2-arm, phase III, randomized, double-blind, placebo-controlled, clinical trial (topical steroid vs Vaseline) (n = 210 patients with head and neck cancer)	Ongoing	
Statins	Anti-inflammatory, immunomodulatory, antioxidant, metabolic, and antibacterial activities	Potentially useful	2
Ghasemi et al, 2018[59]	2-arm, randomized, double-blind, placebo-controlled, clinical trial (topical statin vs placebo) (n = 70 patients with breast cancer)	Reduced grade of RD and patient-reported symptoms	
Trolamine	Nonsteroidal anti-inflammatory; promotes macrophages recruitment and stimulates of granulation tissue	Not proven to be useful	2
Elliott et al, 2006[61]	3-arm, phase III, randomized, multicentered, placebo-controlled, clinical trial (prophylactic trolamine emulsion vs interventional trolamine emulsion vs standard of care) (n = 547 patients with head and neck squamous cell carcinoma)	No difference in grade of RD or patient-reported symptoms	
Fenig et al, 2001[62]	3-arm, randomized, placebo-controlled, clinical trial (Biafine vs Lipiderm vs no treatment) (n = 74 patients with breast cancer)	No benefit in managing RD	

Continued

Table II. Cont'd

Topical agent	Proposed mechanism of action	Clinical efficacy	Level of evidence*
Gosselin et al, 2010[63]	4-arm, prospective, randomized, double-blind, placebo-controlled, clinical trial (trolamine vs placebo vs Aquaphor vs RadiaCare) (n = 208 patients with breast cancer)	No benefit in managing RD	
Abbas and Bensadoun, 2012[64]	2-arm, phase III, randomized, placebo-controlled clinical trial (trolamine vs supportive care) (n = 30 patients with head and neck squamous cell carcinoma)	Reduced grade of RD	
Sucralfate	Acts as a mechanical barrier; antibacterial; anti-inflammatory and promotes angiogenesis	Not proven to be useful	2
Wells et al, 2004[66]	3-arm, randomized, controlled, clinical trial (sucralfate vs no cream) (n = 357 patients with head, neck, breast, or anorectal cancer)	No difference in grade of RD or patient-reported symptoms	
Falkowski et al, 2011[67]	1-arm, prospective study (sucralfate only) (n = 21 patients with breast cancer)	No difference in grade of RD	
Kouloulias et al, 2013[68]	Nonrandomized study using historical control group (sucralfate only) (n = 30 patients with breast cancer)	Reduced grade of RD	
Silver sulfadiazine	Antimicrobial	Potentially useful	2
Hemati et al, 1997[73]	2-arm, randomized, single-blinded, placebo-controlled clinical trial (SSD cream vs control) (n = 102 patients with breast cancer)	Reduced grade of RD	
Silver nylon dressings	Anti-inflammatory, barrier-enhancing	Proven to be useful	2
Vuong et al, 2004[74]	1-arm, prospective, single-blind, study (silver leaf nylon dressing only) (n = 15 patients with anal or gynecologic cancer)	Reduced grade of RD	
Graham et al, 2007[75]	2-arm, phase III, randomized, single-blind, placebo-controlled, clinical trial (SCND vs standard skin care) (n = 196 patients with breast cancer)	Reduced grade of RD	
Niazi et al, 2011[76]	2-arm, phase III, randomized, single-blind, placebo-controlled, clinical trial (SCND vs standard skin care) (n = 42 patients with rectal or anal cancer)	Reduced grade of RD	
Aquino-Parsons et al, 2010[77]	2-arm, phase III, randomized, single-blind, placebo-controlled, clinical trial (SCND vs standard skin care)	Reduced grade of RD	

Manufacturers: Eucerin, Beiersdorf, Hamburg, Germany; Aquaphor, Beiersdorf, Hamburg, Germany; Vaseline, Unilever, Rotterdam, The Netherlands; Biafine, Genmedix Ltd, France; Lipiderm, G-Pharm Ltd, France; RadiaCare, DelSite, Inc, Irving, TX.
CoA, Coenzyme A; *EGCG*, epigallocatechin-3-gallate; *EGF*, epidermal growth factor; *GM-CSF*, granulocyte-macrophage colony-stimulating factor; *HA*, hyaluronic acid; *RCT*, randomized controlled trial; *RD*, radiation dermatitis; *SCND*, silver clear nylon dressing; *SSD*, silver sulfadiazine.
*Level of evidence is based on the Oxford Centre for Evidence Based Medicine 2011 levels of evidence.[78]

metabolic, and antibacterial properties.[54-56] They have been found to improve skin disorders such as psoriasis, dermatitis, uremic pruritus, vitiligo, and hirsutism[55] and promote wound healing in diabetic ulcers.[57,58] In considering the role of topical statins in RD, Ghasemi et al compared topical atorvastatin with placebo, demonstrating that topical atorvastatin significantly decreased radiation-induced breast swelling (as determined by increase in cup size), itching, and pain by factors of 1.8, 1.7, and 1.5, respectively.[59]

Trolamine

Trolamine is a topical oil-in-water emulsion that is largely used in clinical practice for RD management in European countries. It is thought to function as a nonsteroidal anti-inflammatory through macrophage recruitment and stimulation of granulation tissue.[60] Multiple RCTs conducted between 2000 and 2010 found no significant advantage of trolamine over basic supportive care, such as aloe vera, petroleum jelly, lipid-based cream, or placebo, in treating RD.[1,61-63] However, a more recent study

conducted by Abbas et al demonstrated superiority of a trolamine emulsion over supportive care in a small trial, showing a decreased frequency of RTOG grade 3 dermatitis among patients with head and neck squamous cell carcinoma.[64] Further, it is important to note that when compared with β-sitosterol, trolamine was less effective in managing patient-reported symptoms.[30]

Sucralfate

Sucralfate, a basic aluminum salt of sucrose octasulfate, is a common antiulcer medication when administered orally. In topical formulations, sucralfate has demonstrated strong barrier abilities, antibacterial activity, anti-inflammatory effects, and angiogenesis-promoting capabilities.[65] Three studies assessing the clinical efficacy of sucralfate in treating RD have been performed, with variable results. In the largest and best-executed of these studies, sucralfate was not beneficial in reducing the severity of dermatitis or relieving patient-reported symptoms.[66] Falkowski et al demonstrated similar results.[67] On the other hand, Kouloulias et al found beneficial effects of sucralfate in a small, nonrandomized study.[68]

METALLIC OINTMENTS AND DRESSINGS

SSD

Silver sulfadiazine (SSD), a sulfa derivative topical antibacterial, is primarily used as a topical cream for second- and third-degree burns. SSD has also been shown to have anti-inflammatory properties and barrier-enhancing functions, thereby protecting the skin from infectious agents.[69-72] When used for the management of RD, SSD demonstrated a lower total RTOG dermatitis grade when compared with controls ($P < .001$).[73]

Silver nylon dressing

Silver nylon dressing, a nonadherent nanocrystalline material, has traditionally been used in clinical practice as a burn wound dressing. More recently, however, studies have demonstrated that silver nylon dressing assists in managing radiation-induced skin toxicity.[74-77] Specifically, studies have found silver nylon dressings to be superior in lowering the mean dermatitis score when compared with SSD[76] and to be superior in decreasing itching, pain, and burning when compared with the standard of care (which included steroids, moisturizing agents, and SSD).[75,77]

PROPOSAL FOR A TREATMENT ALGORITHM

On the basis of the strength of the evidence for efficacy of treatment in RD, we propose the following treatment algorithm, which utilizes a combination approach. Clinicians should recommend daily washing with mild soap and water to all patients who are receiving radiation treatment (level 2 evidence). Further, all radiotherapy patients should apply a midpotency, topical corticosteroid, such as mometasone furoate (as studied by Ho et al) twice a day from the first day of RT until 2 weeks following the end of RT (level 1 evidence).[52] Clinicians may also wish to recommend silver nylon dressings (level 2 evidence) to be used daily throughout and 2 weeks after RT. For additional symptomatic relief, clinicians can encourage patients to try calendula, β-sitosterol, HA, statins, and SSD (on the basis of level 2 evidence); catechins and GM-CSF (on the basis of level 3 evidence); and EGF (on the basis of level 4 evidence) to avoid the negative effects of overuse of topical steroids. We implore clinicians to discuss these options with each patient and use a trial-and-error approach to determine which topical agent provides the greatest symptomatic relief and is most preferred.

CONCLUSION

This review has identified many topical agents studied in the management of acute RD (Table II).* Washing with mild soap and water and use of topical corticosteroids and silver nylon dressings have proved effective in managing the severity of RD and the associated symptoms. Several other agents, including calendula, catechins, β-sitosterol, HA, EGF, GM-CSF, statins, and SSD, may potentially be useful in managing acute RD, as respective studies have demonstrated positive results. However, additional, confirmatory studies are needed before asserting their clinical efficacy. Finally, this literature review found that aloe vera, chamomile, ascorbic acid, pantothenic acid, trolamine, and sucralfate have not been proved useful in the management of RD.

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