

Treatment of radiation fibrosis

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ABSTRACT

In this review, radiation fibrosis and the challenges investigating therapies for this condition are discussed. The review includes consideration of clinical trial design of empirical therapies tested in the clinic and the translation of pre-clinical strategies of targeted treatments into the clinical setting.

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Key words: Radiation fibrosis; TGFβ1; CTGF

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INTRODUCTION

Cancer survivorship initiatives highlight the need for strategies to manage the consequences of cancer treatment, including fibrosis occurring after curative radiotherapy (<http://www.ncsi.org.uk/>). Although evidence exists for effective treatment for radiation fibrosis, there is no therapeutic strategy of proven benefit. In order to define novel therapeutic strategies for treatment of radiation fibrosis, better understanding of the pathogenesis of radiation related normal tissue injury is required, such that targeted treatment strategies can

be defined, but the greatest hurdle is in translating this step into the clinic. In this review, the challenges of designing effective clinical strategies for testing anti-fibrotic treatments and specifically for the introduction of targeted treatments into clinical trials will be discussed.

THE CHALLENGES OF TRIAL DESIGN IN TREATMENT OF RADIATION FIBROSIS

It is recognised that there is a great unmet need to find an effective anti-fibrotic drug for both radiation fibrosis and fibrotic disease of other aetiologies^[1]. Clinical and preclinical models to study radiation fibrosis have demonstrated that there are reversible and irreversible components^[2-4]. The majority of clinical research in this area has investigated empirical anti-fibrotic treatments for which the mechanism is largely unknown. The use of drugs targeting specific pro-fibrotic pathways are more easily studied in pre-clinical systems and this approach has confirmed that the pro-fibrotic pathway is indeed targetable. The challenge remains in translating these successful pre-clinical studies into the clinic by introducing effective treatment for radiation fibrosis, which does not cause undue toxicity.

Radiation fibrosis affecting an organ may co-exist with other pathologies such as oedema, inflammation and vascular injury. Clinical studies in this area employ defined endpoints such as the Late Effects Normal Tissues Subjective, Objective, Management, Analytic (LENT SOMA) scale^[5] to measure response to anti-fibrotic therapy, which are highly clinically relevant as they encompass patient related scores. However the spectrum of symptoms experienced by the patient may be broad and the relationship of symptomatology to the underlying pathology is complex. This type of clinical trial using scoring alone does not shed light on the exact pathophysiology of the underlying process, nor the tissue response to therapeutic intervention. This is in part because of the difficulty of including translational endpoints involving repeat tissue biopsies. To some extent this can be addressed by using surrogate endpoints for fibrosis, including radiological imaging^[6]. Selecting clinical endpoints which relate directly to fibrosis and can therefore be used

to monitor the treatment of fibrosis itself is therefore challenging. This is an important limitation to conducting successful clinical trials to investigate radiation fibrosis.

A further challenge in this disease is the heterogeneity of radiation injury expressed at the clinical level and probably also the tissue level. This implies that studies may need to include large patient numbers to see a statistically significant effect. Furthermore the clinical endpoint examining the reduction in rate of clinical change in this progressive condition, may be clinically relevant but difficult to demonstrate.

STRATEGIES TO IMPROVE CLINICAL SIDE EFFECTS OF RADIOTHERAPY

Adverse effects of radiotherapy may not be directly attributable to radiation fibrosis. Therefore, in practice, it is likely that combined approaches using therapies to target the fibrotic pathway will be used, at the same time employing supportive strategies which do not directly target fibrosis, to improve patients' symptoms. For example, it is possible to optimise symptoms after pelvic radiotherapy using simple investigation and treatment algorithms for co-existing pathologies such as bile salt malabsorption or bacterial overgrowth^[7]. Similar supportive therapies for fibrosis affecting the musculoskeletal system may be of benefit^[8].

CLINICAL EXPERIENCE OF ANTIFIBROTIC THERAPIES

Treatment strategies for radiation fibrosis have been summarised in reviews by Delanian and Lefaix^[3,9]. These were: (1) anti-inflammatory treatment with corticosteroids or interferon gamma; (2) vascular therapy with pentoxifylline or hyperbaric oxygen; and (3) antioxidant treatment with superoxide dismutase, vitamin E (alpha-tocopherol), and with a pentoxifylline and vitamin E combination. The reviewers comment that the most efficacious has been the pentoxifylline and vitamin E combination (summarised in Table 1). Other treatments tested in the clinical setting in soft tissue fibrosis include other empirical anti-fibrotic drugs, hyperbaric oxygen and pirfenidone (Table 2).

The therapies tested in radiation fibrosis are supported by a body of clinical literature, principally made up of anecdotal reports and data from small studies, whereas positive evidence from well-conducted randomized controlled trials is lacking. As the most widely tested treatment, the combination of pentoxifylline and vitamin E therapy and its use in clinical studies will be discussed in the next section.

PENTOXIFYLLINE AND VITAMIN E

Pentoxifylline and vitamin E are considered to show synergy in the clinical setting. Both drugs have antioxidant properties and each has additional putative mechanisms to explain their action. For example, pentoxifylline, a drug used in vascular disease, improves blood flow, reduces thrombotic effects and has anti-inflammatory and antifibrotic actions. Experimentally the drugs are also synergistic, and have recently been shown to act on the transforming growth factor β 1 (TGF β 1) pathway, inhibiting transcriptional activation of TGF β 1 in smooth muscles cells isolated from patients with radiation enteropathy^[10].

Clinical trial data for pentoxifylline and vitamin E combinations is conflicting. The challenges of designing high quality trials and assessing clinical response in radiation fibrosis, as outlined

above underlie this issue. The majority of clinical data come from small single arm studies which tend to show benefit in improving fibrosis^[2,11-15], whereas randomised controlled trials have tended to be negative^[16] (Table 1). In the majority of these trials, patients were treated for 6 months or less duration, whereas evidence also exists that longer duration therapy is claimed to be necessary to achieve sustained benefit^[14].

Given these limitations there have been important trials in which the investigators have been able to make some conclusions about therapeutic efficacy of empirical treatments in radiation fibrosis. The reported negative trials have contributed to this field, by illustrating the challenges inherent to investigating and treating this disease.

Subcutaneous fibrosis (subheading)

Much of the clinical data on pentoxifylline and vitamin E has come from Sylvie Delanian's group, with evidence for therapeutic efficacy for this drug combination without significant toxicity. An important example of their work was a positive single arm study investigating pentoxifylline and vitamin E in patients with radiation fibrosis, treated with radiotherapy for breast cancer up to 18 years previously^[14]. The majority of women received 24-48 months of therapy, but a smaller earlier cohort received 6-12 months, prior to clinical experience suggesting that longer duration therapy may be better. The primary endpoint was regression of superficial fibrosis, assessed by clinical palpation of the area of superficial induration. The secondary endpoint was clinician assessed SOMA scores. The data demonstrated that even patients treated many years previously with radiotherapy have a response to this drug combination but that this response is slower than in patients who received radiotherapy more recently (up to 6 years previously). The shorter duration therapy was associated with a greater rebound effect with a 40% increase in surface area fibrosis measurement per year. The study therefore suggests a positive treatment effect for this drug combination and demonstrates responses to pentoxifylline and vitamin E in patients treated many years after radiotherapy historically considered to have irreversible disease. The authors conclude that the additional benefit of longer duration therapy means that a commitment for both the clinician and patients to maintain therapy for around 2 years to achieve sustained benefit. The majority of other studies presented in Table 1 used shorter duration therapy (6 months or less).

John Yarnold's group conducted a study of pentoxifylline and vitamin E in patients who had received radiotherapy to the breast or chest wall and nodal areas for breast cancer up to 41 years previously^[16]. The investigators defined a 4 point scale to measure palpable superficial fibrosis, one of the secondary endpoints. Lymphedema was selected as the primary endpoint, assessed using a perometer, as this was considered to be a more objective measurement. Patient self assessments were included as a secondary endpoint in the study design.

The results of the trial showed no significant change in arm volume at 12 months compared to base line for the treatment (2.5%) compared to placebo groups (1.2%). Furthermore, there were similar numbers of responses in placebo and treatment arms. In terms of patient assessed scores, no patients reported benefit. The study also showed no benefit in terms of reducing palpable superficial fibrosis.

The possible reasons for the negative trial were considered by investigators. The group questioned the validity of clinician measurements as the investigators were not blinded to baseline measurement when assessing post treatment timepoints, possibly explaining the responses seen in the placebo group. Delanian et al. showed similar findings in an earlier study of pentoxifylline and

Table 1 Clinical studies of vitamin E and pentoxifylline.

Tissue/organ	Therapy	Ref.	Dose and route of drug administration	Duration of drug	Study phase and design	Number analysed	Time since radiotherapy (years, unless specified)	Tumour site/site of irradiation	Outcome
Soft tissue	Pentoxifylline	[12]	Pentoxifylline 400mg tds, oral	8 weeks	Single arm open label	27	1-29	Head and neck, thorax, spine, chest wall, pelvis, upper and lower limb	Positive
		[11]	Pentoxifylline 400mg tds, oral	3 months (and additional 1 month for responders)	Single arm open label	6 for fibrosis (26 all radiation injuries)	Not specified	Neck and chest wall, axilla, head and neck	Positive
		[2]	Pentoxifylline 400mg bd and Vitamin E 500 IU bd, oral	6 months and for duration of clinical regression in responders	Single arm open label	43	Median 8.5	Head and neck, breast	Positive
Soft tissue	Pentoxifylline and vitamin E	[15]	(A) Pentoxifylline 400mg bd and Vitamin E 500 IU bd; (B) pentoxifylline and placebo; (C) placebo and Vitamin E; (D) placebo-placebo, oral	6 months	Double blind randomised placebo controlled, 2x2 factorial design	22	Mean 7	Breast	Positive
		[14]	Pentoxifylline 400mg bd and Vitamin E 500 IU bd, oral	Long treatment 24-48 months and short treatment 6-12 months	Single arm open label	44	1-18	Breast	Positive
		[16]	(A) Pentoxifylline 400mg bd and dl-alpha tocopheryl acetate 500 mg bd; (B) placebo, oral	6 months	Double blind randomised placebo controlled	68	Median 15.5 (range 2-41)	Breast	Negative
		[13]	Pentoxifylline 400 mg bd and dl-alpha tocopheryl acetate 500 mg bd	6 months	Single arm open label	23	Median 35 (range 17-138)	Pelvis	Positive
Pelvis	Pentoxifylline and vitamin E	[10]	Pentoxifylline 400 mg bd and dl-alpha tocopheryl acetate 500 mg bd	6-24 months	Single arm open label	10	Not specified	Pelvis	Positive

Table 2 Other clinical studies in radiation fibrosis.

Therapy	Ref.	Dose and route of drug administration	Duration of drug	Study phase and design	Number analysed	Time since radiotherapy (years, unless specified)	Tumour site/site of irradiation	Outcome
Grape seed proanthocyanidin extract, IH636 GSPE	[26]	(A) IH636 GSPE 100 mg tds, PO; (B) placebo, oral	6 months	Double blind randomised placebo controlled	66	Mean 10.8	Breast	Negative
Cu/Zn superoxide dismutase	[27]	Liposomal superoxide dismutase (Lipsod) prepared from bovine Cu/Zn superoxide dismutase, 5mg twice weekly, oral	3 weeks	Single arm open label	34	Mean 56 months (range 13-216 months)	Head and neck, prostate, testis, mediastinum, spine, pelvis	Positive
Hyperbaric oxygen	[28]	30 exposures, 5 days a week	6 weeks	Single arm open label	19	Median 2 (range 1 month - 34 years)	Breast	Positive
	[29]	5 days a week until 3 consecutive sessions showed no further improvement	Median number of exposures 25, range 7-60	2 arm, non randomised, open label	44	Median 13 months (range 2-149 months)	Breast	Positive
Pirfenidone	[19]	Pirfenidone 800 mg tds, oral	2 years	Single arm open label	5	Range 32.1-276.5 months	Head and neck, thorax	Positive

vitamin E in which mean regression of superficial palpable fibrosis (area) was 60 % in the treatment group and 43 % in the placebo group after 6 months of treatment^[15].

A further question raised in the study by Gothard *et al.* is the choice of using lymphoedema as an endpoint of radiation fibrosis. The pathogenesis of lymphoedema is uncertain and mechanisms other than fibrosis may be contributory to this clinical problem. Therefore the lack of clinical benefit does not necessarily equate to lack of anti-fibrotic activity at the pathological level. The median duration of swelling for patients in this trial was also many years, possibly refractory to antioxidant therapy at this point, although this question is debatable in view of the late responses seen in the study described above. It is however still possible to conclude that this treatment combination does not show benefit in lymphedema as assessed by clinician and patient endpoints.

Pelvic toxicity (subheading)

The challenge of evaluating therapeutic efficacy of pentoxifylline and vitamin E is addressed by comparison of two similar clinical studies. John Yarnold's group studied pelvic toxicity using 6 months of combination therapy with pentoxifylline and vitamin E in a single arm study^[13]. The LENT SOMA scores used included those relating to both bowel and other pelvic endpoints such as bladder and sexual function. Patient assessed scores were also used. This study showed improvement in LENT SOMA scores, but not in patient assessed scales. The positive findings of improvement in LENT SOMA was interpreted cautiously by the authors in view of the small patient number studied. As previously discussed another methodological flaw in this trial was the lack of blinding of baseline scores, so that baseline and follow-up SOMA scores were not independent. Again arguably, the more important endpoint of patient self-assessment showed no improvement with treatment.

A positive study of pentoxifylline and vitamin E in radiation enteropathy tested the drug combination in 10 consecutive cases with radiation enteropathy, treated for 6-24 months^[10]. Five of the patients also received mesalazine and nitrofurantoin. LENT SOMA scores relating to bowel function were selected as the primary endpoint, and a significant improvement of mean SOMA scores was demonstrated. This shows encouraging data but the limitations of a single arm trial, in which it is not stated if baseline SOMA scores have been blinded, and in which additional treatments used could provide additional confounding, should be interpreted with caution.

TRANSLATION OF TARGETED TREATMENTS IN RADIATION FIBROSIS

Important examples exist of successful targeting of signalling pathways of radiation fibrosis in *in vitro* and *in vivo* pre-clinical models, but these targeted therapies have yet to show efficacy in the clinic. Examples of pre-clinical models and the different potential for their effective translation are discussed.

Pravastatin modulates activation of endothelial cells after irradiation and targets the Rho/ROCK pathway, modulating expression of connective tissue growth factor (CTGF), a pro-fibrotic cytokine^[4]. Pravastatin has been shown to successfully reverse fibrosis at the tissue level in the pre-clinical, *in vivo* setting^[4]. In this model a loop of rat small bowel was treated with a single 19 Gy fraction of radiation. Pravastatin was introduced into the rat's diet at 5 weeks, at the time of established fibrosis and was continued for 10 weeks. The authors describe the pathology as fibronecrosis, characterised by deposition of extracellular matrix components and

an inflammatory infiltrate. Improvement of this pathological lesion, with reduction in collagen tissue density was seen at 26 weeks in rats treated with pravastatin compared to control rats. Furthermore, the investigators show with immunohistochemistry, reduced expression of CTGF in rats given pravastatin compared to those receiving placebo at both 15 weeks and at 26 weeks, validating the target. Modulation of the same pathway by pravastatin was demonstrated in human explants and smooth muscle cells derived from patients with radiation enteropathy showing applicability to human disease. This is a drug class with wide clinical experience and well established toxicity profiles and the investigators have therefore been able to introduce this therapy directly into Phase II clinical trials.

The TGF β pathway is one of the central pathways in radiation fibrosis and has been extensively studied in pre-clinical *in vivo* models. Targeting this pathway in radiation fibrosis leads to therapeutic benefit in animals. Using a rat model of pulmonary fibrosis occurring after radiation, the TGF β pathway has been successfully targeted with a neutralising antibody to TGF β 1^[17]. In this prevention study, the therapy was administered after the final fraction of radiation, given as 8 Gy per fraction for 5 days. The endpoints studied included histological change in the lungs and alteration of TGF β 1 and downstream signal transduction proteins. The investigators compared 4 groups of animals, as follows: sham irradiation, rats receiving the control antibody post irradiation with no therapeutic intervention, and the antibody administered at two dose levels after irradiation. Assessment carried out at 26 weeks showed reduced disruption of alveolar anatomy and collagen deposition, and reduction of TGF β 1 and its downstream signalling transduction proteins in mice receiving the higher dose of antibody compared to control.

This study demonstrates the potential of using an antibody against TGF β to protect against development of radiation induced lung injury, another example showing proof of principle that these pathways are relevant to the pathogenesis of radiation fibrosis *in vivo* and can be targeted. However the translation of this target into the clinic remains more challenging than for the Rho/ROCK pathway for which there the drug, pravastatin is already in routine clinical use. The challenge of targeting the TGF β pathway is demonstrated in a report of diffuse cutaneous systemic sclerosis, an idiopathic disorder leading to skin and lung fibrosis and renal injury in which TGF β 1 is implicated^[18]. In a multicentre study, 45 patients with diffuse cutaneous systemic sclerosis were administered CAT-192, an antibody against TGF β 1. As TGF β 1 has pleiotropic effects, the investigators used an antibody which differed from the pre-clinical model in that only partial blocking of the TGF β 1 axis was intended, due to concerns about safety. Although there was improvement in the score used to measure skin thickness in scleroderma, this finding was independent of treatment group (including placebo) and other functional outcomes to assess renal and pulmonary disease were unchanged.

New anti-fibrotic drugs targeting TGF β 1 and CTGF are in the initial stages of development^[1] and may have application to radiation fibrosis. There is future potential therefore for targeting these pathways in radiation fibrosis.

TRANSLATION OF TARGETED TREATMENT IN IDIOPATHIC FIBROSIS

Clinical data from studies looking at efficacy and toxicity of anti-fibrotic drugs in fibrosis of other aetiologies is potentially helpful in informing about potential treatment strategies for radiation fibrosis.

Idiopathic pulmonary fibrosis (IPF), a progressive fibrotic disease of the lung with a survival of 3-5 years is an example where clinical studies have been particularly active.

Pirfenidone is a p38 kinase inhibitor which modulates TGF β 1 expression. Clinical experience of this drug in radiation fibrosis is limited to one small single arm trial^[19]. The drug was assessed in soft tissue fibrosis, using range of movement and patient assessed scores. Only 5 patients were assessable in this study, and 4 out of 5 of these showed benefit. In IPF, there has been extensive clinical experience of pirfenidone, including a large collaborative study combining data from 2 randomised controlled trials, involving 800 patients^[20]. The primary endpoint was mean change in percentage predicted FVC, which was -8.5% in the treatment arm compared to -11% in the placebo group in a pooled analysis of the two trials. Disease specific survival was 4% ($p=0.03$). The data in IPF supports this drug as being an effective anti-fibrotic agent. It is however of note that the difference in mean change in percentage predicted FVC was small in the treatment and placebo groups and large patient numbers were needed to demonstrate this difference. Furthermore clinical experts in this area debate the clinical significance of these small changes^[21].

Drugs inhibiting receptor tyrosine kinases, a relevant target in radiation fibrosis^[22-24], are also in development. BIBF-1120 is a receptor tyrosine kinase inhibitor targeting the platelet derived growth factor, vascular endothelial growth factor and fibroblast growth factor receptors. There is clinical experience with BIBF-1120 in IPF, as an anti-fibrotic agent, and also cancer where the drug is used due to its anti-angiogenic properties. For IPF, phase III data is awaited, but the drug has shown promising activity in phase II studies in reducing the decline in lung function and preserving quality of life.

CONCLUSIONS

Randomised clinical trial data in the treatment of radiation fibrosis is lacking, although evidence from single arm trials suggest that there may be benefit from empirical anti-fibrotic therapies in this condition. Factors challenging the design of good clinical trials include the broad spectrum of radiation pathologies, the clinical spectrum of toxicities, the inherent difficulties in measuring response and the challenges in setting up clinical trials with sufficient power.

To successfully treat radiation fibrosis in the clinic, good therapeutic targets are needed, and so far, examples of potential strategies have been successfully identified in pre-clinical models. For effective clinical translation, good drugs are also needed which have efficacy, clinically meaningful responses and acceptable toxicity profiles. Ultimately well-designed clinical trials, and collaborative working will be important to achieve this.

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CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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