Prolonged Adverse Events Following Photodynamic Therapy: Regulatory Implications

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ABSTRACT

Objective: To determine whether field photodynamic therapy (PDT) of actinic keratoses (AKs) using a novel preparation of 5-aminolevulonic acid (ALA) would result in fewer subsequent invasive skin cancers developing on the face.

Design: A prospective multi-center randomized controlled trial. The protocol was approved by the Bond University Human Research Ethics Committee in accord with the TGA's Clinical Trial Notification Scheme. The trial was registered (12609000025235) on the Australian New Zealand Clinical Trials Registry.

Setting: Six centers in four states in Australia.

Protocol: Two treatments of ALA PDT, 2 weeks apart for each patient. Controls were observed. Patients were followed up with biopsies of any suspicious lesions every 6 months for 2 years.

Main Outcome Measure(s): Development of new skin cancers.

Results: The trial was suspended after 3 months and closed after 6 months after ethics committee approval was withdrawn on the basis of a breakdown in trial governance. Over the following 2 years, some investigators noted and formally reported the continued occurrence of serious adverse events in excess of those described with other approved cutaneous PDT treatments. USA dermatologists with experience managing AKs with FDA approved ALA products subsequently confirmed prolonged and severe adverse events in 6 of the former trial intervention patients.

Discussion and Conclusions: Adverse effects experienced by patients using the investigational ALA PDT appeared more severe than those experienced when an FDA-approved ALA product is used. We believe the former should be further evaluated for safety. It is of concern that this ALA product and lamp could be promoted and used widely in Australia following these reports of significant adverse events and continued lack of TGA approval.

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BACKGROUND

Photodynamic therapy (PDT) has become an established option in the management of actinic keratoses (AKs) and other skin diseases. Cutaneous PDT has predominantly involved the use of methyl aminolevulinate (MAL) and 5- aminolevulinate (ALA). Products containing MAL and ALA are applied to the affected skin and a light source is then applied to the skin for an illumination following an incubation period. ALA and MAL are absorbed and intracellularly converted to protoporphyrin IX, a light-reactive intermediary protein. Activation of protoporphyrin IX by the PDT light source creates free radicals which is the essential to the mechanism of action.

Lehmann[1] compiled a literature review of PDT for AKs. Complete response rates using MAL for AKs ranged from 69% to 93% at 3 months. This non-invasive treatment option is associated with minimal risk of scarring. Phototoxic reactions that often occur during treatment rapidly heal to produce excellent therapeutic and cosmetic results. The side-effects of therapy are predominantly local phototoxic effects (burning, stinging and prickling sensations). These adverse events are usually mild-to moderate in intensity, of short duration, and easily managed. Lehmann concluded that overall, the efficacy and low risks afforded by this therapy resulted in high patient preference in clinical trials. The efficacy and side effect profile of PDT is broadly similar with MAL and ALA.[2] Active ALA has been demonstrated to be effective when compared with vehicle control.[3] More importantly, no prolonged or permanent adverse events have been reported to date following treatment with either ALA or MAL.

Tierney mailed a questionnaire to 45 patients who received PDT for AKs in 2005-2006.[4] Patients compared PDT with other options. PDT was found to have equivalent or improved recovery times, cosmetic outcomes, patient satisfaction and preferred as a treatment for AKs. In particular, duration of adverse events was significantly shorter in patients managed with PDT compared with cryotherapy or surgical excision. Kaufmann demonstrated that both cryotherapy and PDT are very effective in treating AKs, with patients generally preferring PDT, which produces better

cosmetic outcomes.[5] Hadley reported superior results managing actinic keratoses with PDT than with imiquimod.[6]The illumination of the active ingredient can be effected with proprietary lights, but daylight has also been proven to be effective to activate MAL.[7,8]

To date, the research supporting usage of topical PDT treatment to manage AKs pertains predominantly to Metvix® / Metvixia® (Galderma, Lausanne Switzerland), brands of MAL which use a red light, and the Levulan® (DUSA, Wilmington, Massachusetts USA) brand of ALA which uses a blue light. The Metvix® cream has been approved by the Australian Therapeutic Goods Administration (TGA), the Australian equivalent to the FDA. To our knowledge, no ALA preparations have been evaluated by the TGA. Levulan® is the only ALA approved by the FDA. This product has a patented, somewhat complex delivery system composed of two breakable chambers containing the active ingredients. These are crushed within a tube allowing the ingredients to mix immediately before application.

The trial ALA (tALA) product used to treat the patients described herein was marketed and sold by Allmedic Pty Ltd in 2008 as a novel, simpler, premixed preparation for treating AKs and was promoted as having a prolonged shelf life and requiring a reduced intensity of activating light. This new, commercially available product appeared to offer a more affordable and effective management of AKs with the expectation of only mild and short-term adverse events.

Aim of Study

A prospective randomized controlled trial protocol was approved by the product sponsor who provided the tALA and light source. It was designed as a post-marketing study to investigate whether tALA could result in fewer subsequent skin cancers in patients who had previously had a facial skin cancer. It was not designed as a safety and primary efficacy study, as the sponsoring company reported that these studies had already been completed. Two authors (AD and SA) participated

METHODS

The protocol was approved by the Bond University Human Research Ethics Committee (BUHREC) in accord with the TGA's Clinical Trial Notification (CTN) Scheme.

The trial was registered (12609000025235) on the Australian New Zealand Clinical Trials Registry (ANZCTR) where full methodology details are available. The primary trial sponsor was Allmedic Pty Ltd (Taren Point, NSW, Australia).

The trial began at multiple treatment centers in Australia in January 2009. Patients who had suffered one or more biopsy-proven facial skin cancers were randomized offsite into management with tALA versus observation. No placebo treatment was utilized. All patients had baseline photographs of their face taken.

The intervention protocol involved two PDT treatments, 14 days apart. Following a test dose, tALA was applied to the whole face (except for eyelids and near mucosal surfaces)] followed by a 5-hour incubation period during which facial exposure to light was avoided. Then, a 30-minute facial illumination was performed with the PDT light source provided by the sponsor. The illumination involved the use of a narrow band blue LED light for 20 minutes followed by a narrow band LED red light for 10 minutes. During illumination, the patients' eyes and eyelids were shielded. Each patient had an attendant present at all times during illumination. A fan to reduce burning sensations was provided as required.

Following treatment, the treated patients were given extensive advice regarding minimizing sun exposure, analgesia, and topical care. All patients were scheduled for re-evaluation every 6 months for 2 years following randomization. Patients were advised to request additional appointments if they noted side effects or skin lesions that required attention. At follow-up, photographs were to be taken to assess the clearance rate of AKs and any facial lesion suspicious for skin malignancy was to be biopsied.

RESULTS

Shortly after commencing tALA treatment, several problems were encountered regarding trial governance. In March 2009, following discussions with investigators and the ethics committee, the trial was suspended and no further patients were recruited. The trial was formally discontinued by the sponsor in June 2009. Over the following twelve months, some investigators noted the occurrence of serious adverse events in excess of those previously reported with other cutaneous PDT treatments. These adverse events were reported to the sponsor, ethics committee and the TGA as they were identified and at the 12-month study review.

To better determine whether the study results and adverse events were consistent with usage of US-ALA, American dermatologists experienced in the management of AKs with US-ALA were invited to examine and / or comment on the adverse events reported in 6 of the study patients (affected patients). American dermatologists were involved as Levulan® is not available in Australia. One of the dermatologists (JM) voluntarily assessed 4 of the 6 affected patients 15 to 18 months after their treatment experiences. The examinations occurred face to face in Australia in July 2010. Several medical practitioners also attended as observers. The patients' examinations were visually and audibly recorded with written consent from the patients. Another USA-based dermatologist (HS) reviewed the video recordings from the 4 patients examined, along with available photographs from the adverse event reports of all 6 affected patients, and compared these outcomes with his experience with the US-ALA product.

Of the 34 patients who underwent PDT at this trial center, the 6 affected patients were examined. This site recruited more patients than any other trial site. The affected patients adhered to the trial

FIGURE 1. An 84-year-old male, 2 weeks following treatment.

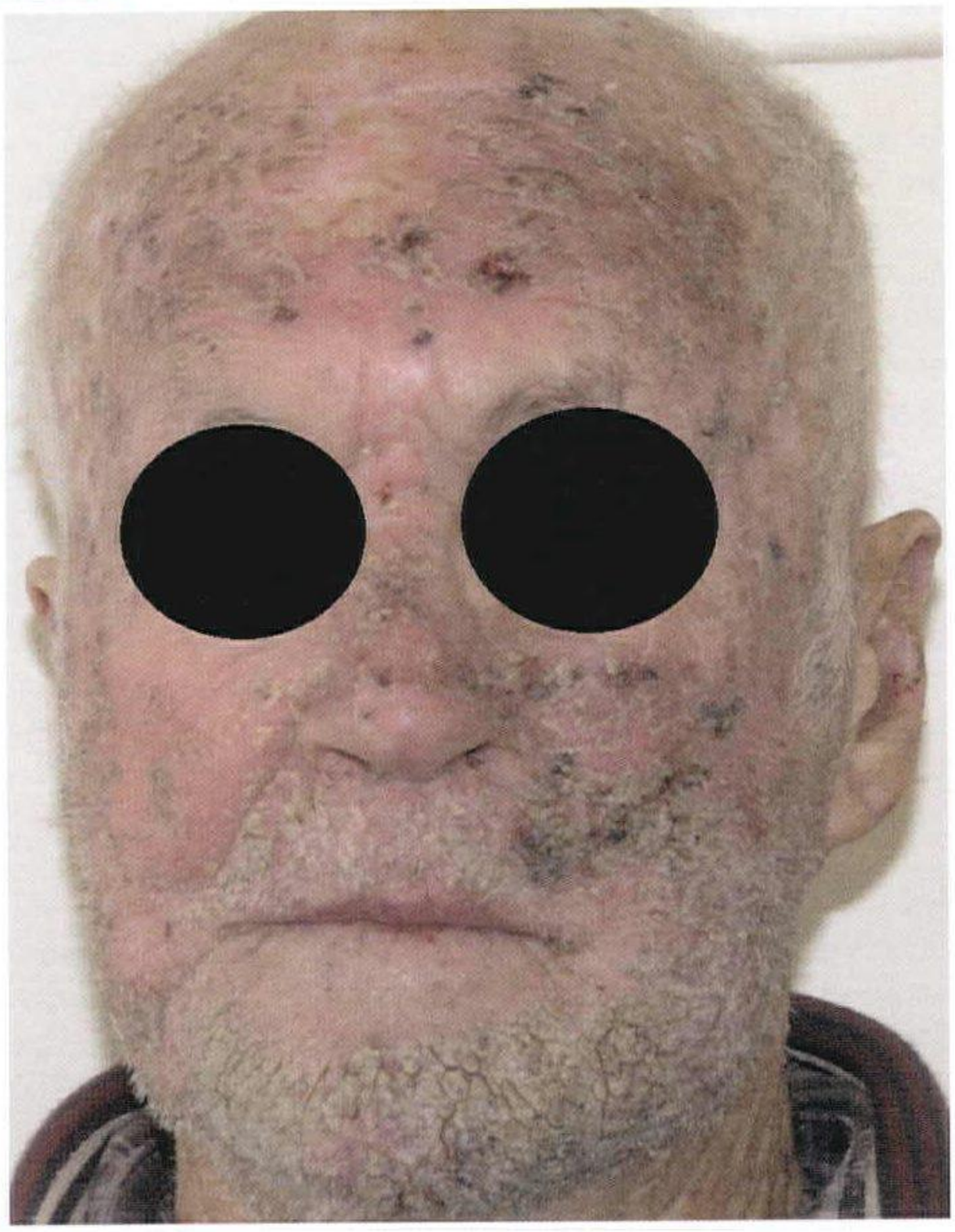
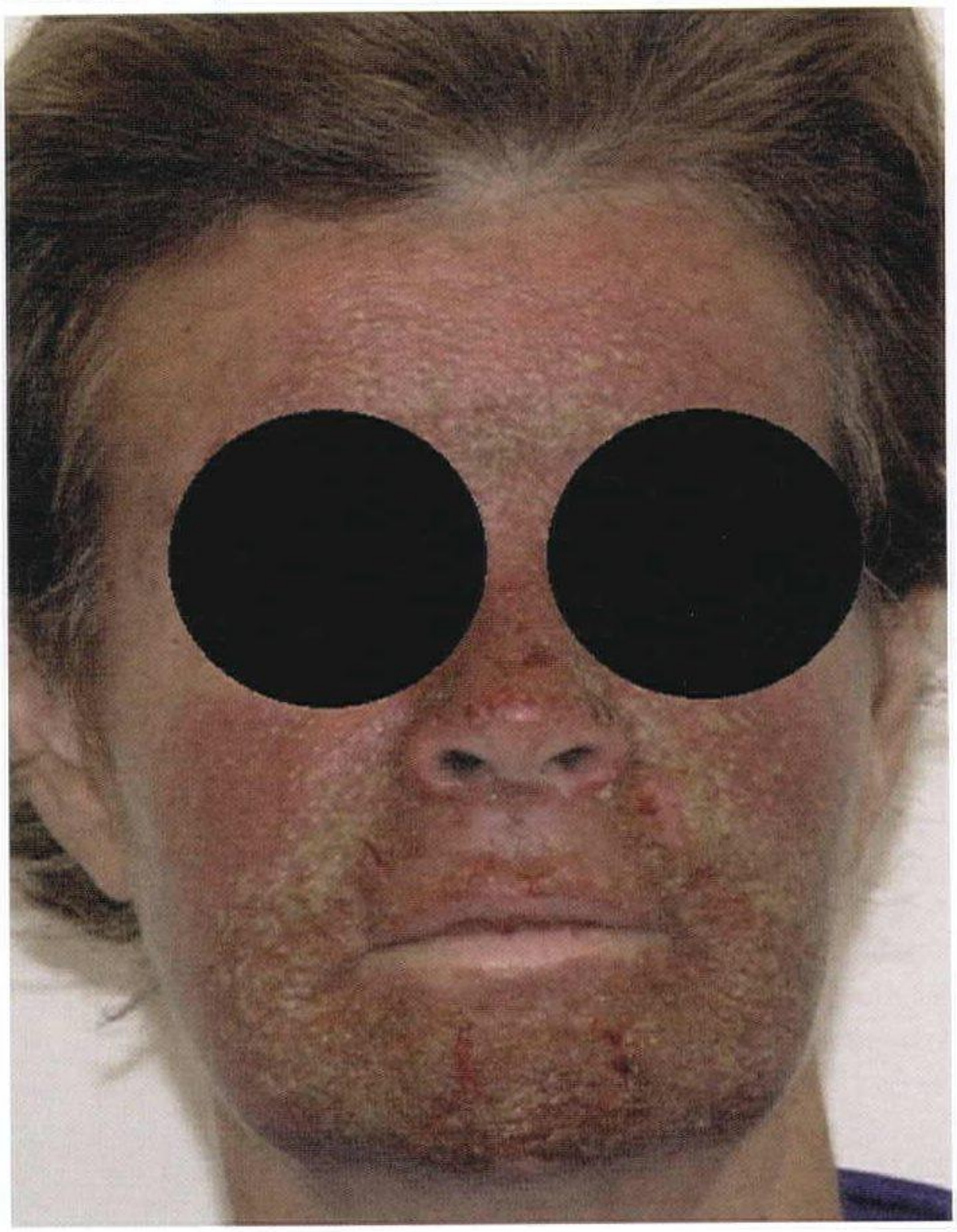


FIGURE 2. A 49-year-old female, 1 week following treatment.



protocol including avoidance of sun in days following treatment. The brief case studies of the 6 Caucasian patients are as follows:

1. A 66-year-old male reported that he had suffered severe chronic back pain and had undergone numerous back operations. Subsequent to tALA treatment, he experienced blistering, crusting and peeling for more than 4 weeks with erythema lasting for 7 weeks. Significant facial photosensitivity precluded him from leaving his house for many weeks. He described 6 to 7 weeks of pain and rated the pain as similar to the worst pain he had ever experienced, including his previous back pain.

2. A 60-year-old male noted pain for 6 weeks following treatment and marked skin peeling over his face.

3. An 84-year-old retiree, with severe facial actinic damage, suffered deep burning pain during illumination, which persisted for several days. He developed multiple facial skin fissures, bullae, and erosions followed by crusting, especially prevalent on the chin, lips, left cheek and forehead. Figure 1 depicts his appearance 2 weeks following treatment. The ulcer present on the left lower forehead healed with a permanent scar. He experienced intermittent, sharp, pains on his chin for several weeks. He was unable to leave his home for 2 to 3 weeks due to facial photosensitivity.

4. An 83-year-old female was unable to tolerate the full 30 minutes of illumination due to severe pain. She reported severe burning, crusting and peeling for 2 to 3 weeks post treatment. Post treatment pain was described as the worst pain she had experienced. Over the counter analgesic medications were ineffective and cool compresses were only minimally effective. Photosensitivity prevented her leaving her home for at least 4 weeks. Two lesions on her upper lip and chin healed with permanent scarring.

5. A 49-year-old female had minimal background actinic damage to her face. Like other trial participants she was recruited because she previously had skin cancer on her face. She was seen one week following treatment for extensive erythema, blistering, crusting, and open sores. These subsided over several weeks, (Figure 2). Photosensitivity prevented outdoor exposure for many weeks. Eighteen months following treatment, she had vertical scars and dysesthesia on her chin. Light touch sensation to the chin region was absent.

6. An 83-year-old developed blistering, crusting and erythema on his face which lasted several weeks. He also developed cellulitis and was treated with combination oral antibiotics. Antibiotic response was initially poor and he was considered for intensive care management.

Both USA-based dermatologists consulted considered the side effects observed following tALA PDT use to not be consistent with those reported for FDA-approved US-ALA PDT. They observed that the prolonged and severe adverse effects experienced by these patients, including pain, photosensitivity, crusting, blistering, peeling, scarring and dysesthesia were more severe and prolonged than cases treated with US-ALA and MLA.

The bottles of tALA provided for the trial were not labelled with their composition or expiry dates, and the manufacturer declined to provide this data. We have not been able to find published safety or efficacy studies on the tALA, and after termination of the study, the investigators learned that the product had not been approved by the Australian TGA. The tALA continues to be promoted, supplied and used in Australia by some physicians. The TGA have stated that they are investigating these matters.

DISCUSSION

A number of patients treated with the trial ALA in the current study experienced adverse effects that were more severe and prolonged than those observed with another FDA approved US-ALA preparation. The US-ALA involves use of a blue light source whereas the tALA involved illumination with both blue and red lights. Blue light has a shorter wave length, and therefore less dermal penetration, than red light. As such, the possible deeper dermal activation with the tALA may be a factor in the more severe adverse events noted. Given that all 6 reported affected patients were treated at the same site, another possibility is that the batch of tALA used at this site was not consistent with other batches. The lack of batch labelling on the tALA means that this cannot be investigated further. To our knowledge these are the first confirmed and reported cases of permanent scarring following topical PDT.

The authors had been informed by the sponsor of the study that preliminary safety and efficacy studies had been completed and reported to the appropriate authorities. It is unfortunate that these studies had not been completed and the tALA and lamp provided for the study were not approved by the appropriate authorities. The tALA and lamp continue to be promoted for use by medical practitioners in Australia. The adverse effects documented in the current paper have been previously reported to the sponsoring company, the TGA and BUHREC. It is also worrying that the authors cannot find literature or details of any previous studies using the commercially-available ALA preparation provided by the sponsor for the study.

There is increasing concern that healthcare practitioners often make decisions on the basis of incomplete and/or biased subsets of trial results; such partially informed decision-making can compromise patient care. There are issues regarding medical treatments sold by doctors whereby doctors stand to profit from recommending such treatment. It has been suggested that doctors have their objectivity distorted when they stand to profit from selling a treatment rather than prescribe a treatment supplied by a pharmacy.[9] A significant financial outlay is required for the medical light device needed to perform PDT. Might this cause some physicians who have made this outlay to be less likely to accept negative opinions and adverse events reported about the treatment?

This trial demonstrates the potential for poor patient outcomes as well as the inappropriate sale and marketing of health products when regulatory authorities in other countries do not meet the rigorous standards of the USFDA.

Investigating doctors were advised and believed that the tALA and lamp provided by the sponsoring company was an established, proven and approved ALA-PDT therapy. This trial was indeed an aftermarket study to investigate the potential for reduction in new skin cancers. In retrospect, the investigators believe that they may have been naive in assuming due diligence by the company supplying products?

Allmedic describes itself "as an Australian Medical Skin Health company founded and operated by medical doctors who specialize and practice in the fields of skin cancer, medical cosmetology, molecular immunology, and skin allergies."[10] Are doctors more likely to accept claims made about a product when the source is a colleague?

The authors are concerned that despite attempting to highlight the concerns raised above through appropriate channels, it is now left to an ad hoc group of investigators and others, who, after the fact, wave the flag and bring the issue of such a major health concern forward.

CONCLUSION

Based on our past experience and the information obtained through our face-to-face interviews with the affected patients, we consider that the tALA-PDT therapy provided for this trial does not have a clinical expectation consistent with that of the US-ALA product. It is clear that inadequate evidence of this product's safety and efficacy exists in the public domain. We are concerned that Australians and others may be exposed to potential harm by a product not adequately evaluated and regulated. We also believe that this report demonstrates the importance of proper vetting by government regulatory agencies before new treatments may be investigated in clinical trials and are approved for use. It also demonstrates that physician investigators must undertake their own due diligence before participating in clinical trials.

DISCLOSURES

Family interests of author AD have shares in the sponsoring company. This holding has and is being managed independently with all profits (if any) directed to independent medical research.

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