Photodynamic therapy for dysplastic Barrett’s oesophagus: a prospective, double blind, randomised, placebo controlled trial

R Ackroyd, N J Brown, M F Davis, T J Stephenson, S L Marcus, C J Stoddard, A G Johnson, M W R Reed

Abstract

Background and aims—Photodynamic therapy (PDT) is a treatment in which cell damage is achieved by the action of light on a photosensitising agent. We have assessed the potential use of PDT in the ablation of Barrett’s oesophagus.

Methods—Thirty six patients with dysplastic Barrett’s oesophagus receiving acid suppression medication with omeprazole were randomised to receive oral 5-aminolaevulinic acid (ALA) 30 mg/kg or placebo, followed four hours later by laser endoscopy. Follow up endoscopy was performed at one, six, 12, and 24 months.

Results—Of 18 patients in the ALA group, a response was seen in 16 (median decrease in area in the treated region 30%; range 0–60%). In the placebo group, a decrease in area of 10% was observed in two patients with no change in 16 (median 0%; range 0–10%; treatment v placebo, p<0.001). No dysplasia was seen in the columnar epithelium within the treatment area of any patient in the PDT group. However, in the placebo group, persistent low grade dysplasia was found in 12 patients (p<0.001). There were no short or long term major side effects. The effects of treatment were maintained for up to 24 months.

Conclusions—This is the first randomised controlled trial of PDT for Barrett’s oesophagus. It demonstrates that ALA induced PDT can provide safe and effective ablation of low grade dysplastic epithelium.

Keywords: Barrett’s oesophagus; photodynamic therapy; aminolaevulinic acid; protoporphyrin IX

The incidence of oesophageal adenocarcinoma is rapidly increasing in the western world. A major risk factor is Barrett’s oesophagus, an acquired condition in which squamous mucosa is replaced by metaplastic columnar epithelium. The incidence has been estimated as 1 in 50 to 1 in 441 patient years.12-14 The risk is increased with dysplasia; in particular, high grade dysplasia (HGD) is considered a precursor of malignancy, and therefore an indication for endoscopic therapy in suitable patients.1 4

Current therapeutic approaches aim to decrease oesophageal acid exposure by pharmacological or surgical means. However, despite the efficacy of medical treatment in symptom control and ulcer healing, there is little evidence that it produces regression of Barrett’s epithelium. Results of antireflux surgery demonstrate regression in 40% of patients in one study,5 and squamous island formation in another,6 but others failed to show any regression.7–9

Another approach is photodynamic therapy (PDT) which involves administration of a photosensitising drug followed by application of light to produce cell damage. The most commonly used photosensitiser is haematoporphyrin derivative (HpD), which has been used in the treatment of early dysplasia and carcinoma in Barrett’s oesophagus, although treatments have been complicated by stricture formation due to excess depth of tissue damage.10 Overholt reports the use of PDT using sodium porphyrin and red light in the treatment of 100 patients with dysplasia and superficial carcinoma in Barrett’s oesophagus.11 Mucosal ablation and squamous re-epithelialisation was seen in 75–80% of treated Barrett’s mucosa, with complete elimination in 43 cases. Areas of dysplasia were eliminated in 78 patients and 10 of 13 malignancies were ablated. However, healing was associated with stricture formation in 34%.

A novel approach to PDT is endogenous photosensitisation with aminolaevulinic acid (ALA), a naturally occurring compound in the haem biosynthetic pathway. This has no innate photosensitisation properties but is metabolised to the photosensitive compound protoporphyrin IX (PpIX). This has several advantages over HpD, in particular a reduced duration of photosensitisation and an affinity for epithelial tissues. This results in a more selective effect in the gastrointestinal mucosa, with less damage to underlying muscle thus reducing the risk of stricture and/or perforation.

ALA induced PDT has been used in the treatment of both dysplastic Barrett’s oesophagus and oesophageal carcinoma.12–14 In a report of five patients with HGD in Barrett’s oesophagus treated with ALA induced PDT, elimination of HGD and squamous regeneration was seen in all patients. There were no complications or recurrence of dysplasia after treatment.15

Abbreviations used in this paper: PDT, photodynamic therapy; ALA, aminolaevulinic acid; LGD, low grade dysplasia; HGD, high grade dysplasia; HpD, haematoporphyrin derivative; PpIX, protoporphyrin IX; Nd:YAG, neodymium-yttrium aluminium garnet; KTP, potassium titanyl phosphate; MPEC, multipolar electrocoagulation; ABPC, argon beam plasma coagulation.
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26–44 months of follow up but in two cases persistent non-dysplastic columnar glands were found beneath the neo-squamous epithelium.13

More recently, in a report of 32 patients with HGD (n=10) or mucosal cancer (n=22) in Barrett’s oesophagus treated with ALA induced PDT, dysplasia was eradicated in all patients (10 of 10) and mucosal cancer in 17 of 22 (77%) at a mean follow up of 9.9 (range 1–30 months). All tumours up to 2 mm in depth were completely ablated (17 of 17). There was no morbidity or mortality.14

While these studies demonstrate the feasibility of ALA induced PDT as treatment for Barrett’s oesophagus, they are uncontrolled series and there have been no randomised controlled trials. This study aimed to assess the efficacy of PDT in the ablation of Barrett’s oesophagus in a prospective, double blind, randomised, placebo controlled trial with observer blinded endoscopic and histological assessment of treatment response. The trial aimed to exclude placebo response due to laser light related hyperthermia or the effect of drug alone (omeprazole or ALA), and to eliminate avoidable sources of bias, such as observer error. We assessed not only the macroscopic effect on Barrett’s mucosa but also the histological effects on dysplasia and the issue of “buried” glands seen in other studies, and attempted to establish the duration of treatment response. Treatment parameters were those established in a previous pharmacokinetic study of PpIX production after two different oral doses of ALA at three different time points.15 16

Patients and methods

After ethics committee approval was obtained, appropriate patients were sought from endoscopy and histopathology records. Patient recruitment took place throughout 1995, and eligibility was restricted to patients with low grade dysplasia (LGD) in circumferential Barrett’s oesophagus of at least 3 cm in length who were receiving omeprazole. Patients were identified and the histology was re-examined by a single experienced gastrointestinal histopathologist (TJS) to confirm the diagnosis. Barrett’s oesophagus was diagnosed only when specialised columnar epithelium (with intestinal metaplasia) was seen.17 Dysplasia was defined as neoplastic epithelium confined within the basement membrane in the absence of inflammation, and was classified as LGD according to accepted criteria.17 18 The histological diagnosis was confirmed on biopsy, no more than six weeks before treatment.

TREATMENT PROTOCOL

All treatments were performed as day cases. Patients were randomised to receive 30 mg/kg ALA or placebo. The randomisation was performed 1:1 by opening of one of a series of 36 previously sealed envelopes. This was done by pharmacy staff and the outcome was unknown to clinical staff and patients. ALA was dissolved in 50 ml of orange juice or placebo was provided (orange juice alone). ALA is tasteless and so the treatment group could not detect the drug in their drink. Four hours after ALA or placebo administration, laser endoscopy was performed under intravenous sedation and analgesia (midazolam, pethidine, and propofol) administered by an anaesthetist. ALA dose and interval between ALA and light administration were selected on the basis of a previous dosimetric study.15 16

Once the patient was sedated, endoscopy was performed using an Olympus Q10 endoscope (Olympus Optical Co. Ltd, Tokyo, Japan). At this time, the length and percentage of the circumference of the oesophageal wall covered by Barrett’s columnar epithelium was recorded, from which the area involved was calculated. All longitudinal measurements were taken from the upper incisor teeth (or gum) and confirmatory photographs were taken.

Light delivery was generated by a copper vapour laser (Oxford 20 Watt, Oxford Lasers, Abingdon, UK) and delivered via a fibre with a diffuser tip (Laserscope Flex Cylinder Diffuser, PDT Systems Inc., Santa Barbara, California, USA). Uniform oesophageal light distribution was achieved using an applicator, consisting of a 14 mm diameter clear perspex cylinder attached to the end of an Atkinson tube introducer with a central channel 3 cm in length, housing the diffuser tip of the laser fibre. Before and after treatment, the light delivery system was calibrated using an integrating sphere, and throughout treatment light delivery was monitored by means of an isotropic detector fibre incorporated in the applicator.

The light applicator was lubricated and introduced over an endoscopically positioned guidewire into the oesophagus. It was positioned by means of 1 cm calibrated markings along the outer sheath so that the 3 cm “treatment window” was situated at the area of the oesophagus to be treated, as determined by measurement from the incisor teeth (or gums). Because of the size of the applicator it was not possible to check endoscopically the position of the light delivery system under direct vision.

All patients were treated with green light (514 nm) at a power density of 120 mW/cm² for a period of 500 seconds per 3 cm length. Temperature was monitored by a thermocouple in the applicator. Each therapy consisted of two separate treatments (distal then proximal; total treatment time 1000 seconds; energy density 60 J/cm²) so that a total of 6 cm (2×3 cm) length of oesophagus was treated, coinciding with the upper 6 cm of Barrett’s mucosa. A 6 cm treatment represented complete treatment of Barrett’s epithelium in 18 of 36 (50%) patients.

If the Barrett’s segment was between 3 and 6 cm, two treatments were still performed. If tongues of columnar epithelium were observed above the area of circumferential Barrett’s, the area to be treated was measured from the apex. This led to some areas of normal mucosa being included in the treatment area but this was necessary for complete treatment of the 6 cm length of Barrett’s. If the length of Barrett’s oesophagus was greater than 6 cm, no further
Table 1 Demographic details and treatment outcome in patients who received aminoalaevulinic acid-photodynamic therapy

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Pretreatment endoscopy findings</th>
<th>Post-treatment endoscopy findings</th>
<th>Post-treatment histology</th>
<th>Percentage area regression</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>63</td>
<td>9 cm circumferential Barrett's</td>
<td>7 cm circumferential Barrett's</td>
<td>Normal squamous</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>30</td>
<td>6 cm circumferential Barrett's</td>
<td>5 cm streaky Barrett's</td>
<td>Normal squamous</td>
<td>50</td>
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<tr>
<td>3</td>
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<td>52</td>
<td>6 cm circumferential Barrett's</td>
<td>4 cm Barrett's with islands+++</td>
<td>Squamous/ Barrett's</td>
<td>10</td>
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<tr>
<td>4</td>
<td>M</td>
<td>58</td>
<td>13 cm Barrett's + 1 cm tongue</td>
<td>13 cm Barrett's with islands</td>
<td>Normal squamous</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>49</td>
<td>6 cm circumferential Barrett's</td>
<td>2 cm Barrett's + 3 cm streaks</td>
<td>Squamous / Barrett's</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>54</td>
<td>6 cm Barrett's + 1 cm tongue</td>
<td>6 cm circumferential Barrett's</td>
<td>Normal squamous</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>53</td>
<td>13 cm Barrett's + 1 cm tongue</td>
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<td>Normal squamous</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>58</td>
<td>4 cm Barrett's + 1 cm tongue</td>
<td>3 cm Barrett's + 2 cm streaks</td>
<td>Normal squamous</td>
<td>40</td>
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<tr>
<td>9</td>
<td>F</td>
<td>71</td>
<td>4 cm Barrett's + some islands</td>
<td>3 cm Barrett's + 2 cm streaks</td>
<td>Normal squamous</td>
<td>30</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>53</td>
<td>4 cm Barrett's + 1 cm tongue</td>
<td>3 cm Barrett's + islands+++</td>
<td>Normal squamous</td>
<td>30</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>64</td>
<td>6 cm circumferential Barrett's</td>
<td>4 cm Barrett's + 2 cm tongue</td>
<td>Normal squamous</td>
<td>30</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
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<td>4 cm Barrett's + 1 cm tongue</td>
<td>2 cm Barrett's + 2 cm tongue</td>
<td>Normal squamous</td>
<td>30</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>69</td>
<td>10 cm Barrett's + 2 cm tongue</td>
<td>10 cm Barrett's + 2 cm tongue</td>
<td>Normal squamous</td>
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<td>Normal squamous</td>
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<td>M</td>
<td>54</td>
<td>7 cm Barrett's + 2 cm streaks</td>
<td>5 cm Barrett's + 2 cm tongue</td>
<td>Normal squamous</td>
<td>60</td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>59</td>
<td>2 cm Barrett's + 3 cm streaks</td>
<td>4 cm streaky Barrett's</td>
<td>Normal squamous</td>
<td>30</td>
</tr>
</tbody>
</table>

Sections were stained with haematoxylin and cosin and examined both by the routine hospital histopathology service and again by a single experienced gastrointestinal histopathologist (TJS) who was blinded to the other histological analyses and to the randomisation group of the patient.

**STATISTICAL ANALYSIS**

Before patients were recruited, a power calculation was performed using a commercially available software package (In Stat, Version 2.01, Graph Pub Software, San Diego, Califor-nia, USA). It was calculated that to show a 30% difference in outcome (as predicted from previous open studies) at a significance level (two sided) of p<0.05 and a power of 90%, 16 patients would be required in each group.

Patient demographics and pretreatment findings were analysed using either a χ² or two tailed Mann-Whitney U test, as appropriate.

The outcome of treatment was assessed in two ways. Both the proportion of responders and mean percentage of area regression were calculated for each of the two groups. Statistical analysis was performed using the SPSS for Windows (version 6.0) software package. To compare the proportion of patients responding in each group, a 2x2 comparison was made using a χ² test. The percentage area regression was assessed by two tailed Mann-Whitney U test. Statistical significance was taken at p<0.05.

**Results**

Of 70 patients initially thought to have LGD in Barrett’s, the diagnosis was confirmed in 45 on expert pathology review. Of these, 36 patients (30 male, six female; median age 56 (range 30–71) years) agreed to enter the study, of whom 18 were given 30 mg/kg ALA and 18 received placebo. The two groups were demographically similar, with 15 men and three women in each and a median age of 56 (range 30–71) and 54 (range 44–68) years, respectively. Both had similar pretreatment lengths of Barrett’s, with a median total length of 6 cm (range 4–15) and 7 cm (range 3–15), respectively (tables 1, 2). Nine patients refused to take part in the study, five for family reasons and four claiming that they wished to see that treatment was performed and any residual disease was left untreated. This was because the combination of the inflexibility and diameter of the introducing system and duration of treatment required to treat longer segments was considered inappropriate, particularly as the aim of the study was to study the effect of PDT rather than totally eradicate all traces of Barrett’s oesophagus.

Following treatment, patients were given analgesia and antiemetics as required and were allowed to eat and drink as soon as they were able. They remained in hospital until dark and were then allowed home, with appropriate oral analgesia and a supply of antacids to take as necessary. Patients were advised to avoid bright light for 24 hours.

**FOLLOW UP PROTOCOL**

Throughout treatment and the whole of the follow up period (two years), patients were maintained on omeprazole 20 mg daily. Follow up endoscopic assessments were performed at one, six, 12, and 24 months after treatment. The length and percentage of the involved circumference were recorded, from which the area was calculated.

At each visit, endoscopy was performed by two independent observers, neither of whom was aware of the patient’s randomisation group, and both were blinded to the pretreatment assessment and to each other’s assessment. Subsequent comparisons were made between the pre- and post-treatment assessments, and the two post-treatment assessments, from which the effect of treatment and degree of interobserver variation in endoscopic interpretation of Barrett’s oesophagus was assessed. In each patient, the percentage change in area was recorded to the nearest 10%, as it is not possible to quantify this to any greater degree. Only on final statistical analysis was the mean percentage area reduction calculated to the nearest 1%.

Six biopsies were taken from the treated area for histological analysis at six, 12, and 24 months to confirm whether true regression from columnar to squamous epithelium had occurred and to assess the impact on dysplasia and the presence of buried glands. The biopsies were taken using standard endoscopic biopsy forceps and sent for histological analysis.

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the treatment was effective before agreeing to undergo several endoscopic examinations.

Of the 18 patients given photosensitiser, 16 (89%) showed macroscopic evidence of regression at follow up endoscopy. The median reduction in area within the treated area was 30%. Of the patients given placebo, a macroscopic response was seen in two (11%). In those cases, the area regression was 10%, producing an overall median response of 0% regression (tables 1, 2). There was a statistically significant difference between the two groups (treatment v placebo) in the number of patients responding ($\chi^2=21.8; df 1, p<0.001$; difference in proportions 78%, 95% confidence interval (CI) 56–100%) and in median area regression (median area difference 30%, 95% CI 20–40%; $p<0.001$).

Table 2 Demographic details and treatment outcome in patients who received placebo

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Pretreatment endoscopic findings</th>
<th>Post-treatment endoscopic findings</th>
<th>Post-treatment histology</th>
<th>Percentage area regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>65</td>
<td>6 cm circumferential Barrett's</td>
<td>6 cm circumferential Barrett's</td>
<td>Barrett's with LGD</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>64</td>
<td>10 cm circumferential Barrett's</td>
<td>10 cm circumferential Barrett's</td>
<td>Barrett's with LGD</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>50</td>
<td>5 cm circumferential Barrett's</td>
<td>5 cm circumferential Barrett's</td>
<td>Barrett's; no dysplasia</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>68</td>
<td>10 cm circumferential Barrett's</td>
<td>10 cm circumferential Barrett's</td>
<td>Barrett's with LGD</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>60</td>
<td>10 cm circumferential Barrett's  + 2 cm tongue</td>
<td>9 cm Barrett's + 3 cm tongue Barrett's; no dysplasia</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6</td>
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<td>13 cm Barrett's + 1 cm tongue</td>
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<tr>
<td>7</td>
<td>M</td>
<td>64</td>
<td>2 cm Barrett's + 2 cm tongue</td>
<td>2 cm Barrett's + 2 cm tongue</td>
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<tr>
<td>8</td>
<td>M</td>
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<td>7 cm Barrett's + 2 cm streaks</td>
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<td>Barrett's with LGD</td>
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<tr>
<td>9</td>
<td>M</td>
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<tr>
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<td>F</td>
<td>63</td>
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<tr>
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<td>12</td>
<td>M</td>
<td>67</td>
<td>6 cm circumferential Barrett's</td>
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<td>51</td>
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<td>7 cm circumferential Barrett's</td>
<td>Barrett's; no dysplasia</td>
<td>0</td>
</tr>
</tbody>
</table>

LGD, low grade dysplasia.

Histological examination of the biopsies taken at follow up endoscopy confirmed the macroscopic findings in all cases. In all 16 cases of regression in the treatment group, biopsies from the area of re-epithelialisation displayed normal squamous mucosa, with no evidence of either squamous dysplasia or underlying columnar epithelium. Moreover, biopsies of the remaining columnar epithelium in all 18 cases displayed no evidence of dysplasia in the area that had been treated with PDT. In the placebo group, biopsies from the area of re-epithelialisation in the two cases showing some evidence of regression confirmed the appearance of normal squamous epithelium. Biopsies from the apparently unchanged columnar epithelium displayed Barrett's columnar mucosa in all cases. In 12 of 18 cases, there was persistent LGD but in six patients no evidence of dysplasia was seen (tables 1, 2). With regard to the effect on dysplasia alone, there was therefore a statistically significant difference between the two groups ($\chi^2=18.0; df 1, p<0.001$). In all cases, the underlying submucosa was identified, confirming that the biopsies taken represented full thickness samples.

Discussion
When the present study was designed and implemented (1995), there were no published reports of the effect of ALA-PDT on Barrett's oesophagus. Therefore, we designed a double blind, randomised, placebo controlled trial to address this question. We did not aim to ablate all of the area of Barrett's change in every case for the following reasons:

(i) treatment of segments greater than 6 cm was considered inappropriate because of prolonged treatment times (>16 minutes) due to the unsuitability of the introducing system used in this study. At this time, there was no commercially available balloon catheter; and

(ii) confirmation that ALA-PDT is effective and safe in the ablation of Barrett's oesophagus in this type of study could be used to justify further studies designed to completely eradicate the Barrett's change, using a combination of longer flexible balloon devices and retreatment of unaffected areas. There are now several reports in the literature demonstrating the efficacy of ALA-PDT in the treatment of dysplastic Barrett's oesophagus.11,12 However, the current study remains the only
prospective, randomised, controlled study
to date using treatment parameters estab-
lished in a previous pharmacokinetic
study. We demonstrated a significant difference
between treatment and control groups in all
parameters examined. There was a highly
significant difference in the proportion of
patients responding to treatment, with 90%
and 10% responses in the treatment and
control groups, respectively. There was also a
significant reduction in columnar epithelial
area in the treatment group. The reduction of
Barrett’s by only 30% of the treatment area
and the patchy response within the treatment area
in some patients could be seen as a weakness of
the study. However, as previously stated, we did
not aim to completely ablate the Barrett’s change
in all cases.

In most cases, PDT resulted in streaks or
patches of columnar epithelium rather than
complete circumferential ablation. The reason
for this is unclear, but it may be due to the use
of a solid state applicator with a fixed external
diameter. The internal luminal diameter of the
oesophagus varies within and between patients
and is convoluted unless expanded. The streaks
and patches of columnar epithelium remaining
may be due to mucosal folds not eradicated by
the applicator. Another disadvantage is the
diameter of the applicator used in this study,
requiring sedation for the introduction of the
device. Oesophageal intubation would be
easier with a more flexible device, which could
be passed via the biopsy channel of an
endoscope. The latter may also allow more
accurate placement within the oesophagus,
with less reliance on measurement of the
distance from the incisor teeth, also permitting
direct visualisation during treatment. The use
of a balloon catheter may solve these problems,
but such devices were not readily available at
the onset of the study in 1995. Thus complete
ablation of Barrett’s oesophagus may be
achieved far more readily using a combination
of balloon light delivery devices, multiple treat-
ments at each session, and repeated treatment
sessions. The effect of increased doses of
proton pump inhibitors should also be studied
as this may account for some of the response
seen in regression of Barrett’s change and dys-
plasia in the placebo group.

Dysplasia was successfully eliminated in the
treated area in the PDT group, including the
two cases showing no obvious macroscopic
response, while in the placebo group LGD
persisted in two thirds of cases. The reason for
the apparent elimination of dysplasia in one
third of patients in the placebo group is
unclear. It may have been due to continuing
administration of omeprazole throughout
treatment or to the natural history of LGD
which can spontaneously regress in some cases.
Indeed, it could be argued that it would be bet-
ter to perform a trial such as this using only
patients with HGD, but such patients are less
common and would be harder to recruit.
Equally, it may have been a sampling error at
the time of the biopsy, with Barrett’s epithe-
lium containing only patchy dysplastic
changes. At the time of planning this study, the
value of systematic four quadrant biopsies in
preference to multiple “random” biopsies was
not recognised. However, despite the theoretic-
ical limitation of the biopsy regimen in the cur-
rent study, dysplasia was detected in all
patients before treatment and none after treat-
ment in the PDT group. There was a
significant difference between the two groups,
indicating that ALA-PDT may cause
regression of dysplasia without necessarily
eradicating the associated Barrett’s change.
This unexpected finding has not been reported
previously and requires further confirmation in
future studies.

This trial confirmed the efficacy of ALA
induced PDT in the treatment of dysplastic
Barrett’s oesophagus, the results in the treat-
ment group being similar to those of other
series. A major drawback of treatment seen
in previous studies has been the persistence of
buried columnar glands beneath the neo-
squamous epithelium, with consequent impli-
cations for the remaining cancer risk. This
was not encountered in our study. The reason
for this may be due to the use of green light
which, although it penetrates mucosa less well
than red light, is entirely absorbed within the
depth corresponding to the mucosa, possibly
resulting in a greater PDT effect. Alterna-
tively, it could be sampling error, but this is
unlikely given that each patient had six biopsies
on four occasions after treatment.

PDT is not the only form of ablative therapy
currently under investigation for the treatment
of Barrett’s oesophagus. Thermal photo-
coagulation using neodymium-yttrium aluminium
garnet (Nd-YAG), potassium titanyl phos-
phate (KTP), laser, multipolar electro-
coagulation (MPEC), argon beam plasma
coaigation (ABPC) have been re-
ported. In a report of 16 patients with
non-dysplastic Barrett’s oesophagus treated by
KTP laser and acid suppression, mucosal abla-
tion and squamous regeneration were seen in
all cases. However, in 11 patients there was
evidence of squamous regeneration over re-
mainin Barrett’s glands, and in nine patients
squamous metaplasia was seen within Barrett’s
glands. In another study of 10 patients with
Barrett’s, complete mucosal ablation was
achieved in all cases, but specialised mucosa
was seen beneath the neo-squamous
epithelium. In a report of 24 patients with
Barrett’s oesophagus (six with dysplasia) treated
with ABPC, complete replacement of
Barrett’s mucosa by squamous epithelium was
achieved in 13. However, these results were
achieved with repeated treatments (median 2;
range 1–7). Furthermore there were two
dyspeagheal perforations (one fatal), a problem
not seen in the present study.

Further studies are required to improve the
efficacy of ALA induced PDT. The use of a
balloon catheter may improve clinical outcome
by eliminating folds in the oesophageal mucosa
thereby improving intraoesophageal light dis-
tribution. This study has demonstrated that the
treatment is safe and simple to perform. In light
of this, a protocol of multiple treatments
with the end point of producing complete ablation is required. Finally, randomised, placebo controlled clinical trials are needed to study the use of all types of ablative therapy and there will eventually be a need for prospective randomised trials to compare these different techniques.

This is the first prospective, double blind, randomised, placebo controlled trial of PDT to show effective ablation of dysplastic Barrett’s oesophagus. It was a rigorous and unbiased assessment of this therapy and provides a clear indication of its potential. The majority of patients given photosensitiser and light showed evidence of macroscopic improvement following treatment, and in all cases there was apparent elimination of dysplasia. In contrast with other ablative therapies, or PDT with porphyrin based sensitisers, the low risk of complications renders this a viable treatment for dysplastic and possibly non-dysplastic Barrett’s oesophagus.

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