

Daylight photodynamic therapy: patient willingness to undertake home treatment

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DEAR EDITOR, In the U.K., almost one in four individuals over 60 years are affected by actinic keratoses (AKs),¹ and this is a cause of significant morbidity in an ageing population, with risk of progression to squamous cell carcinoma.² Daylight photodynamic therapy (dPDT) is an effective and simple treatment for field change AK, with similar efficacy to conventional PDT.³ Commonly, skin surface preparation is performed in a dermatology clinic prior to dPDT. However, a recent German study by Karrer and colleagues investigated dPDT as a patient-applied home-delivered treatment for face and scalp AK and reported that patients who undertook this self-administered treatment had high levels of efficacy, tolerance and patient satisfaction.⁴

We surveyed patients who had previously received dPDT at Ninewells Hospital, Dundee to ascertain their experience of treatment, whether they would have liked dPDT sooner, whether they would consider doing the treatment themselves and what type of support they would require (<https://www.researchgate.net/project/Smart-PDT>). A questionnaire was sent to 56 patients and 35 were returned. An engagement event was also held, inviting nine survey participants of differing viewpoints (five attended) and six members of staff to discuss the questionnaire further and investigate potential service improvements (focusing on improving the current service and the potential for home treatment). Formal advice on the construction and content of the questionnaire, and on the organization, content and focus of the engagement event was provided by the National Health Service (NHS) Tayside improvement team, which is part of the Academic Health Science Partnership in Tayside. Approval of the use of the questionnaire and engagement event was obtained through the NHS Tayside local clinical governance process.

Consistent with previous published studies,⁵ most respondents experienced no problems during dPDT (63%) and 90% felt that clearance rates were the same as (32%) or better than (58%) other treatments that they previously underwent for AK. In this secondary care setting, most of our respondents had previously received several types of treatment prior to dPDT (61% 5-fluorouracil, 52% diclofenac, 51% surgery, 45% cryotherapy, 36% imiquimod). A total of 54% of patients reported that dPDT was better tolerated and 27% stated similar tolerance to other AK treatments; although poor weather had caused difficulties for some (low temperature – six responses and rain – five responses). Respondents ranked minimal pain/discomfort, disease clearance, convenience of outdoor treatment and good cosmetic outcome as important factors for dPDT, with 82% being happy or very happy with the service.





It is apparent from our results and published studies that dPDT is a preferred and well-tolerated treatment for AKs.³ It has also been reported that there is poor adherence with other forms of AK treatment.¹ Currently, dPDT is only available in a limited number of locations in the U.K. and often these are secondary healthcare providers. Our respondents would have appreciated the opportunity to have treatment sooner in a non-hospital setting (73%), with 12% preferring dPDT via general practitioner surgeries, 15% could be persuaded to undertake self-treatment, 34% said they would be happy to self-treat if adequate support was available and 12% would like to control and have some ownership of their own treatment.

Respondents were also asked their opinion on using a smartphone application to perform treatment at home and the support they would require using such an application. In total, 50% of respondents said they owned a smartphone or tablet and in order to use the application to perform dPDT at home 78% of respondents would want contact details of a dPDT nurse, while 61% wanted weather predictions and 61% required a step-by-step written guide. Half of respondents wanted the ability to send secure messages to a doctor or nurse, 44% wanted instructional videos (i.e. prodrug application and aftercare) and the same number required the ability to send pictures to the doctors or nurses. Only 11% would want audio instructions, with 17% selecting 'other' and highlighting the desire for accurate dosage reports throughout treatment. From the engagement event it was further clarified that it would be essential for the app to be intuitive and easy to use. The clear message from this event was that patients wanted choice – to have local treatment available or for self-delivery at home.

To our knowledge, it has never previously been demonstrated that there is a willingness within the AK patient population to undertake dPDT treatment at home and to use smart technology to assist in such an endeavour. Our findings highlight the importance to patients of the availability of well-tolerated, effective, convenient treatment for AKs, as well as the high value of including patient opinion in clinical service development.

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Concurrent mucous membrane pemphigoid and membranous glomerulonephritis in a patient with autoantibodies targeting the 1080 region of collagen XVII

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DEAR EDITOR, Mucous membrane pemphigoid (MMP) is a heterogeneous autoimmune disease with subepithelial blistering of mucous membranes and occasionally skin. It is characterized by autoantibodies targeting epidermal basement membrane zone (BMZ) proteins: BP180 (collagen XVII), BP230 (BPAG1), laminin-332, collagen VII and $\alpha 6\beta 4$ integrin. Reactivity to BP180 is predominantly outside the noncollagenous domain 16A (NC16A) region known to be pathogenic in bullous pemphigoid. A documented link exists between pemphigoid disorders and immune-mediated renal abnormalities,^{1,2} but a common mechanism has not been identified. To our knowledge, this is the first report of simultaneous presentation of MMP and membranous glomerulonephritis (MGN).

A 68-year-old man presented with a 1.5-year history of oral erosions and some cutaneous involvement. Direct immunofluorescence (IF) of skin biopsy showed linear deposits of IgG and C3 along the BMZ. Indirect IF revealed linear IgG (titre 1:1280), as well as IgA, reacting exclusively with epidermal side of 1M NaCl-split normal human skin (Fig. 1a). Circulating antibody concentrations were 11.6 U mL^{-1} for BP180 and negative for BP230 (MBL International, Japan, positive test $> 9 \text{ U mL}^{-1}$). The patient's serum reacted positively with recombinant integrin $\alpha 6$ on immunoblot, consistent with MMP. Screening labs were significant for non-nephrotic proteinuria and haematuria. Direct IF of renal biopsy revealed deposition of IgG and C3 in glomeruli. Electron microscopy demonstrated electron-dense deposits along the subepithelial

region of glomerular BMZ. Serum and tissue PLA2R was negative. A diagnosis of MGN was made.

As the commercial BP180 enzyme-linked immunosorbent assay (ELISA) utilizes only the NC16A region, antibodies to other regions are not detected. We evaluated serum reactivity to BP180 using immunoblot of recombinant proteins.³ Strong serum IgG, but not IgA, reactivity was observed to recombinant secreted collagen XVII (sec180) [amino acids (AA) 490–1497] and mild reactivity to NC16A (AA 490–566), consistent with the ELISA results. A similar reactivity pattern was observed in immunoblot against extracts from healthy human skin and kidney; this includes the 100–150 kDa bands produced against the recombinant sec180 (Fig. 1b). To define the regions of specificity, we performed epitope mapping against the following recombinant fragments of BP180: AA 1080–1107, AA 1280–1315 (NC4), AA 1331–1404 and AA 1365–1458. Strong IgG reactivity against AA 1080–1107 and a moderate IgA reactivity against NC4 region was observed. Preabsorption of serum with recombinant 1080 resulted in specific loss of immunoblot reactivity (Fig. 1c) as well as 50% reduction in indirect IF signals. Indirect IF with patient serum against healthy human or mouse kidney did not produce any glomerular staining.

At the time of writing, the patient had three mucous membrane/cutaneous flares, each accompanied by non-nephrotic proteinuria and haematuria. He received three cycles \times 4 doses of 375 mg m^{-2} rituximab. His mucosa and kidney responded each time and he remained in remission for approximately 1.5 years.

The parallel course in severity and treatment response of cutaneous and renal manifestations suggest that in our patient the two-organ involvement may be a result of primary events, although the possibility of secondary MGN cannot be completely ruled out. Consistent with this, his immunoreactants were observed as electron-dense deposits only along the glomerular basement membrane subepithelium on electron microscopy. Evidence suggests that in about 10% of patients with negative PLAR2 (our patient), primary MGN is the result of a still unknown antipodocyte antibody.⁴ Thus, we hypothesized that our patient's autoantibodies cross-react with a common BP180 epitope in both the skin and kidney. Indeed, we identified a similar pattern of reactivity to skin and kidney lysates and using epitope mapping we show IgG reactivity specific to AA 1080–1107 of BP180. These findings are consistent with the recently demonstrated BP180 expression in podocytes of normal mouse and human kidney.⁵

It is possible that our patient had additional renal-specific antibodies, for example his serum reacted strongly with recombinant integrin $\alpha 6$, expressed in both kidney tubules and skin.⁶ Alternatively, the concurrence of mucocutaneous and renal involvement here may be because of patient-specific renal antigen not present on healthy tissue. Anti-collagen IV antibodies have been implicated in the pathogenesis of subepithelial blisters and renal pathology.^{1,7,8} In our patient there was not a reaction with collagen IV recombinant proteins and his glomerular lesions did not contain crescents, the expected presentation with collagen type IV antibodies.