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Doxycycline compared with prednisolone therapy for patients with bullous pemphigoid: cost-effectiveness analysis of the BLISTER trial


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Summary

Background Bullous pemphigoid (BP) is an autoimmune blistering skin disorder associated with significant morbidity and mortality. Doxycycline and prednisolone to treat bullous pemphigoid were compared within a randomized controlled trial (RCT).

Objectives To compare the cost-effectiveness of doxycycline-initiated and prednisolone-initiated treatment for patients with BP.

Methods Quality-of-life (EuroQoL-5D-3L) and resource data were collected as part of the BLISTER trial: a multicentre, parallel-group, investigator-blinded RCT. Within-trial analysis was performed using bivariate regression of costs and quality-adjusted life-years (QALYs), with multiple imputation of missing data, informing a probabilistic assessment of incremental treatment cost-effectiveness from a health service perspective.

Results In the base case, there was no robust difference in costs or QALYs per patient at 1 year comparing doxycycline- with prednisolone-initiated therapy [net cost £959, 95% confidence interval (CI) −£24 to £1941; net QALYs −0.024, 95% CI −0.088 to 0.041]. However, the findings varied by baseline blister severity. For patients with mild or moderate blistering (≤ 30 blisters) net costs and outcomes were similar. For patients with severe blistering (> 30 blisters) net costs were higher (£2558, 95% CI −£82 to £5198) and quality of life poorer (−0.090 QALYs, 95% CI −0.22 to 0.042) for patients starting on doxycycline. The probability that doxycycline would be cost-effective for those with severe pemphigoid was 1.5% at a willingness to pay of £20 000 per QALY.

Conclusions Consistently with the clinical findings of the BLISTER trial, patients with mild or moderate blistering should receive treatment guided by the safety and effectiveness of the drugs and patient preference – neither strategy is clearly a preferred use of National Health Service resources. However, prednisolone-initiated treatment may be more cost-effective for patients with severe blistering.
Bullous pemphigoid (BP) is an autoimmune skin disease characterized by intense itching, erythema, blisters and possible secondary infection. The incidence of BP ranges between 14 and 42 new patients per million in Europe, doubling in the last decade. BP is more common in patients over 70 years of age, and is associated with increased morbidity and mortality. Although oral prednisolone has been the basis of treatment for over 50 years, significant adverse effects in older patients and uncertainty as to optimal dosing are problematic. Whole-body long-term topical use of superpotent topical corticosteroids may be as effective as high-dose oral prednisolone, with lower risk of harm, although this may not be suitable for those with limited mobility or in care. Tetrazyclines have been used in BP for their anti-inflammatory action, although with little supporting evidence. While tetracyclines might be less effective, they are expected to be safer than oral prednisolone.

The Bullous Pemphigoid Steroids and Tetracyclines (BLISTER) trial was designed to provide a pragmatic, definitive comparison of starting treatment with the tetracycline doxycycline (200 mg per day) or starting treatment with oral prednisolone (0.5 mg kg\(^{-1}\) per day). Thus, BLISTER was designed to detect whether an acceptable level of short-term blister control could be achieved with a strategy of starting treatment with doxycycline (noninferiority), while providing increased long-term safety when compared with prednisolone.

In brief, BLISTER was a multicentre, parallel-group, investigator-blind randomized controlled trial, comparing doxycycline and prednisolone-initiated treatment, recruiting 253 adult patients from 54 U.K. and seven German dermatology centres, with a primary efficacy outcome at 6 weeks and a long-term safety outcome at 52 weeks. Patients were also assessed at 13, 26 and 39 weeks. The mean age of participants was 78 ± 10 years, 29% had severe blistering and the groups were similar at baseline. Patients were allowed to switch treatments or alter the dose of prednisolone after the first 6 weeks in order to reflect real-world clinical practice. Topical corticosteroids were allowed in small quantities (< 30 g per week to localized areas for symptomatic relief only) for the first 3 weeks and after 6 weeks.

The noninferiority primary effectiveness outcome was met (the proportion of participants with at most three blisters at 6 weeks): doxycycline 74% vs. prednisolone 91%, an adjusted difference of 19% (90% confidence interval 11–26%) favouring prednisolone. The upper-bound 90% confidence interval of 26% was well within the prespecified margin of noninferiority of 37%. For the safety analysis, treatment-related severe, life-threatening and fatal events over 1 year occurred in 18% of the doxycycline group vs. 36% with prednisolone, an adjusted difference of 19% (95% confidence interval 8–30%). This is clear evidence of increased safety for a treatment strategy of starting with doxycycline. The clinical study found no evidence of interaction between treatment effectiveness and safety according to the severity of disease at baseline (i.e. number of blisters), with severity classified as mild (three to nine blisters), moderate (10–30) or severe (> 30).

Economic analysis informs decision makers about the value for money of treatment alternatives, as healthcare resources are limited and prioritization should consider the efficient use of resources. An economic analysis was conducted as an integral part of the BLISTER study, following a prospective
analysis plan, in order to provide robust evidence of cost-effectiveness to inform health service decision making.

Patients and methods

A within-trial patient-level cost-effectiveness analysis was undertaken comparing doxycycline- and prednisolone-initiated treatment in patients with BP, using data from the BLISTER trial. To quantify the likelihood that either intervention is cost-effective, the effect of treatment changes was estimated as cost and quality-adjusted life-years (QALYs); the analysis was from the U.K. National Health Service (NHS) perspective. As follow-up was limited to 1 year, no discounting of costs and benefits was applied. The analysis followed intention-to-treat principles, in which patients were included in the analysis according to the treatment allocated by randomization, and irrespectively of subsequent care.

Outcomes

Generic health-related quality of life was assessed using the EuroQol questionnaire, a patient-completed two-page questionnaire consisting of the EQ-5D-3L descriptive system and the EQ visual analogue scale (EQ-VAS). The EQ-5D-3L includes five questions addressing mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with each dimension assessed at three levels: no problems, some problems and extreme problems. EQ-5D scores were converted to health status scores using the U.K. time-trade-off value set recommended by the EuroQol group, providing a single health-related index including 0 (death) and 1 (perfect health), where negative scores are possible for some health states. Patients who died during the study were subsequently scored zero at later scheduled follow-up visits for both cost and EQ-5D score and are included as observed data.

The EQ-VAS reports self-rated health on a vertical, visual analogue scale where 100 denotes 'best imaginable health state' and 0 denotes 'worst imaginable health state'. Additionally, the Dermatology Life Quality Index (DLQI) was recorded as a disease-specific measure. The DLQI asks patients 10 questions about how their skin condition has affected their life over the past week, providing an aggregate score in the range 0–30. Quality-of-life measures were captured during clinic visits at baseline and 6, 13, 26, 39 and 52 weeks.

Using the trapezoidal rule, the area under the curve (AUC) of health status scores was calculated, providing patient-level QALY estimates for the cost-effectiveness analysis. Similarly, EQ-VAS and DLQI scores were integrated discretely over time. As AUC estimates were predicted to correlate with baseline scores (and thus potential baseline imbalances), AUC estimates were adjusted for baseline scores.

Resource use and cost

Resource assessments occurred at scheduled clinic visits. Use by patients of study and nonstudy drugs was recorded in the trial drug log. BP-related health service contacts were recorded during clinic visits using patient diaries as an aide-memoire. At clinic visits, all health service resource use was recorded, together with attribution of resources to BP. Patients with no recorded resource use were excluded from the analysis.

Patient costs were estimated in U.K. pounds sterling (2013) as the sum of resources used weighted by their reference costs. Study drugs were prescribed at varying doses and durations. Using national Prescription Cost Analysis (PCA) data, average costs per unit weight of therapeutic agent were determined and applied to patient drug use records: doxycycline £0.0015 per mg and prednisolone £0.0221 per mg. Use of topical steroids was costed similarly using PCA data.

Costs of inpatient stays (in days) and outpatient visits were estimated using Hospital Episodes Statistics (HES) and the National Schedule of Reference Costs. National HES data were explored for inpatient episodes with a primary diagnosis of L12.0 bullous pemphigoid; the 10 most common Health-care Resource Group HRG4+ codes associated with that diagnosis were included, accounting for 96.2% of admissions. Daily costs for each code were estimated from NHS reference costs, and a volume-weighted average cost per admission for BP was estimated allowing for mean stay and cost per day. Inpatient stays cost £334 per day and outpatient attendances were £98 per visit. General practitioner (GP) clinic and home visits, and practice and district nurse visits were costed using unit costs provided by the Personal Social Services Research Unit. Community care contacts were GP (clinic) £46, GP (home) £92, practice nurse £13 and district nurse £39.

Analysis

Follow-up of elderly patients with BP within trials is problematic, and some incompleteness of data was anticipated. Consequently, a base-case analysis was conducted whereby missing data were imputed using multiple imputation. The base-case analysis included the imputed within-trial incremental cost and QALYs gained, adjusted for trial baseline covariates and including use of resources attributed to BP. Supportive sensitivity analyses included only patients with complete data, exploring the impact of imputation, and estimation including all resources recorded regardless of attribution.

The base-case analysis used multiple imputation, conducted according to good practice guidance. Multiple imputation provides unbiased estimates of treatment effect if data are missing at random; this assumption was explored in the data, for example by using logistic regression for missing costs and QALYs against baseline variables. A regression model was used to generate multiple imputed datasets (or ‘draws’) for individual treatment groups, where missing values were predicted drawing on predictive covariates: age, sex, baseline blister severity and baseline Karnofsky score. Outcome measures (at each time point) and costs contributed as both predictors and imputed variables.

Each draw provided a complete dataset, which reflected the distributions and correlations between variables. Predictive
mean matching drawn from the five nearest neighbours (\(k_m = 5\)) was used to enhance the plausibility and robustness of imputed values, as normality could not be assumed. The imputation model used fully conditional (Markov chain Monte Carlo) methods (multiple imputation by chained equations), which are appropriate when missing and correlated data occur in more than one variable. Each draw was analysed independently using bivariate regression (see below) and the estimates obtained were pooled to generate mean and variance estimates of costs and QALYs using Rubin’s rule – a method that captures within and between variances for imputed samples.\(^{31}\) To minimize the information loss of finite imputation sampling, 50 draws were taken, resulting in a loss of efficiency relative to infinite sampling of < 0.5% in all imputed values. The distribution of imputed and observed values was compared visually and statistically to establish that imputation did not introduce bias into subsequent estimation.

Bivariate regression using seemingly unrelated regression equations was used to model incremental changes in costs and QALYs. This method respects the correlation of costs and outcomes within the data, and allows adjustment for a set of covariates, which can be explored and which improve precision.\(^{32}\) Baseline quality-of-life scores were included within all models to allow for potential baseline imbalances.\(^{19}\) Joint distributions of costs and outcomes were generated using the (nonparametric) bootstrap method, with replicates used to populate a cost-effectiveness plane. Bootstrapping jointly resamples costs and outcomes from the original data with replacement (maintaining the sample correlation structure) to create a new bootstrap sample from which changes in costs and QALYs are estimated. Using bias-corrected nonparametric bootstrapping, 5000 bootstraps were taken per model or draw evaluated. Mean estimates are reported with 95% credible intervals (CIs).

The incremental cost-effectiveness ratio (ICER) was estimated as the difference between treatments in mean total costs divided by the difference in mean total QALYs. Value for money is determined by comparing the ICER with a threshold, typically the National Institute for Health and Care Excellence threshold for British studies, of £20 000–£30 000 per QALY.\(^{33}\) This represents the willingness to pay for an additional QALY, and lower values than the threshold could be considered cost-effective for use in the NHS. Base-case assumptions are explored using a range of supportive sensitivity analyses.

The net monetary benefit (NMB) of changing treatment was reported as a recalculation of the ICER at a range of thresholds of willingness to pay for an additional QALY. The NMB succinctly describes the resource gain (or loss) when investing in a new treatment when resources can be used elsewhere at the same threshold. NMB estimates were used to generate cost-effectiveness acceptability curves (CEACs). The CEAC compares the likelihood that treatments are cost-effective as the willingness-to-pay threshold varies.\(^{30}\)

The expected value of perfect information (EVPI) is the upper limit of the value to a healthcare system of further research to eliminate uncertainty.\(^{34}\) Findings from cost-effectiveness analyses remain uncertain because of the imperfect information they use. If a wrong adoption decision (to make a treatment available) is made this will bring with it costs in terms of health benefit foregone; the NMB framework allows this expected cost of uncertainty to be determined and guide whether further research should be conducted to eliminate uncertainty.

Analyses and modelling were undertaken in STATA 14 SE (STATACORP, College Station, TX, U.S.A.). Reporting follows the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.\(^{35}\)

**Results**

**Completeness of data**

Of 253 patients within the clinical trial, 220 (87%) were included in the economic analysis (Table 1). Included and excluded patients were similar in treatment allocation, age, sex, Karnofsky score and blister severity. Of these 220 patients, 164 (75%) had complete EQ-5D assessments for all periods. There was a pattern of decreasing completeness as follow-up proceeded. Resource data were complete for 191 patients (87%). It was not possible to explore completeness of healthcare costs by follow-up visit as patients could use diaries to complete missing data at a later follow-up visit and the study drug report covered the entire follow-up period. When considering both utilities and resource use, complete information was available for 143 patients (65%). Completeness of data was similar when comparing treatment arms (Table 1). Thirty-three patients died during the trial period, 14 (12.5%) in the doxycycline-initiated arm and 19 (17.6%) in the prednisolone-initiated arm, predominantly due to the age and health status and resource use.

<table>
<thead>
<tr>
<th>Health status (EQ-5D)</th>
<th>Prednisolone, (n = 108)</th>
<th>Doxycycline, (n = 112)</th>
<th>Total, (n = 220)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>107 (99.1)</td>
<td>112 (100-0)</td>
<td>219 (99.5)</td>
</tr>
<tr>
<td>6 weeks</td>
<td>102 (94-4)</td>
<td>108 (96-4)</td>
<td>210 (95-5)</td>
</tr>
<tr>
<td>13 weeks</td>
<td>101 (93-5)</td>
<td>101 (90-2)</td>
<td>202 (91-8)</td>
</tr>
<tr>
<td>26 weeks</td>
<td>96 (88-9)</td>
<td>93 (83-0)</td>
<td>189 (85-9)</td>
</tr>
<tr>
<td>39 weeks</td>
<td>94 (87-0)</td>
<td>90 (80-4)</td>
<td>184 (83-6)</td>
</tr>
<tr>
<td>52 weeks</td>
<td>92 (85-2)</td>
<td>90 (80-4)</td>
<td>182 (82-7)</td>
</tr>
<tr>
<td>All visits</td>
<td>83 (76-9)</td>
<td>81 (72-3)</td>
<td>164 (74-5)</td>
</tr>
<tr>
<td><strong>Resource use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug use</td>
<td>95 (88-0)</td>
<td>102 (91-1)</td>
<td>197 (89-5)</td>
</tr>
<tr>
<td>Health service</td>
<td>103 (95-4)</td>
<td>107 (95-5)</td>
<td>210 (95-5)</td>
</tr>
<tr>
<td>contacts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>92 (85-2)</td>
<td>99 (88-4)</td>
<td>191 (86-8)</td>
</tr>
<tr>
<td><strong>Health status and resource use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost and EQ-5D</td>
<td>72 (66-7)</td>
<td>71 (63-4)</td>
<td>143 (65-0)</td>
</tr>
</tbody>
</table>

All values are \(\%\). *EuroQoL-5D-3L index score.
comorbidities of patients. Missing values were imputed to provide a base-case analysis including all 220 patients.

**Complete-case estimates**

Mean EQ-5D scores, resource use and cost data are reported by treatment in Table S1 (see Supporting Information). Over the 52-week follow-up period there were no significant differences in QALYs when comparing the two treatment strategies. Although resource use comparisons (attributed to BP) were generally not significant, there was a pattern of greater care received by patients on doxycycline, consistent with a lower level of clinical effectiveness reflected (by design) in the primary outcome. There was significant, subsequent crossover to the alternative study drug in patients with poor outcomes. Of patients starting on prednisolone, 12.6% subsequently received at least one prescription of doxycycline; of patients starting on doxycycline, 57.8% subsequently received at least one prescription of prednisolone.

Four different types of potent to very potent topical corticosteroids were commonly used; the overall use of any topical corticosteroid during the trial was very similar for patients initiating on prednisolone (76.8%) and doxycycline (72.5%). However, the amount used (and steroid potency) was notably lower in the prednisolone group (average prescribed amount of all topical steroids among users: prednisolone 121 g vs. doxycycline 277 g). Similar proportions of patients received the immunosuppressant azathioprine (prednisolone 4.2% vs. doxycycline 8.8%), although again the amount used was far lower in the prednisolone group (average prescribed amount among users: prednisolone group 2.9 g vs. doxycycline group 12.4 g). Patterns of resource use were costed using national reference values (see Methods: Resource use and cost). Although costs for patients starting on doxycycline treatment appeared greater over 1 year, the increase was imprecise.

**Cost-effectiveness analysis**

The joint distribution of incremental cost and outcome for the base-case analysis is shown graphically in Figure 1. Patients started on doxycycline (compared with prednisolone) experienced a slightly lower average quality of life (−0.024 QALYs, 95% CI −0.088 to 0.041), while tending to incur higher average health costs (£959, 95% CI £24 to £1941) compared with those started on prednisolone, although neither finding was significant (Table S2; see Supporting Information). These findings are consistent with the results of the clinical trial, which demonstrated a compromise between reduced effectiveness and increased safety for doxycycline. The joint distribution of cost and outcome is summarized within the NMB metric. Using a willingness-to-pay criterion of £20,000 per QALY gained, the NMB associated with doxycycline-initiated therapy was negative (−£1432; 95% CI £3094 to £230). Thus, the base-case analysis suggests that NHS resources would be better directed to prednisolone- than doxycycline-initiated therapy in terms of cost-effectiveness. This finding is echoed in the cost-effectiveness acceptability curve, which expresses the NMB finding as a probability (Fig. 2; all patients). The likelihood that doxycycline-initiated treatment is cost-effective is 4.6% given a willingness-to-pay criterion of £20,000 per QALY gained (Table S2; see Supporting Information). Note that one-sided model probabilities should not be compared with inferential findings from (two-sided) statistical tests.

**Sensitivity analyses**

Comparing mean costs and QALY estimates using different modelling assumptions supports the base-case finding (Table S2; see Supporting Information). The qualitative similarity of NMB estimates comparing imputed and complete-case analysis, covariate adjustment and range of costs included...
supports the validity of the imputation process and assumptions.

Subgroup analyses

There was no interaction between treatment effect and trial stratifying variables, except in the case of disease severity. The 63 patients (28.6%) recruited with severe blistering (>30 blisters at baseline) demonstrated a different cost and outcome pattern from patients with mild or moderate disease, as shown in Table S2 (see Supporting Information) and Figure 3. For patients presenting with mild or moderate disease, the differences in costs and QALYs are very small and thus the costs and outcomes can be thought to be similar. For patients presenting with severe disease, doxycycline-initiated treatment results in greater costs (£2558, 95% CI £82 to £5198) and poorer quality of life (−0.090 QALYs, 95% CI −0.22 to 0.042), which together make this strategy appear a poor investment (NMB £4361, 95% CI £8283 to £439) using a willingness-to-pay criterion of £20 000 per QALY gained.

Value of further research

An EVPI analysis was conducted to explore the value of reducing uncertainty about the cost-effectiveness of doxycycline- or prednisolone-initiated therapy. EVPI analysis at the patient
level was conducted treating the two trial strata for index lesion size as independent trials. The remaining value of obtaining perfect information is low (Fig. 4). There remains the greatest uncertainty about the management of patients with mild-to-moderate disease. In 2012, 1018 patients were hospitalized in England with a primary diagnosis of BP. Within the trial, 71-4% of patients presented with mild-to-moderate disease based on the number of blisters present at screening: if generalizable then the treatment of 727 patients a year might be affected by greater certainty about treatment. Assuming the findings affected care for 10 years the population affected might number 7270, taking an EVPI of £242 per patient. The population EVPI is £176 000, a fraction of the average cost of a nationally recruiting multicentre clinical trial (undiscounted costs). Taking into consideration the particular difficulties of conducting trials in this patient group, there may not be scope to conduct a further definitive trial in patients with mild-to-moderate disease.

Other end points

The three quality-of-life measures used in the BLISTER trial are reported in Table 2. EQ-VAS, like EQ-5D, provides a 1-year approximation of quality-adjusted survival for each treatment group. EQ-VAS is scored 0–100; equivalent QALY scores are obtained by dividing by 100, although EQ-VAS is not recommended for QALY estimation within trials, as values are preference rated rather than societal. DLQI is scored 0–30; the average score over the 1-year follow-up period is reported, using the AUC between the three time points to calculate the average. Being a disease-specific quality-of-life measure, the DLQI is potentially more sensitive to change than a generic measure; nonetheless, the changes correspond to an average of 1 point on a 30-point scale and are of uncertain clinical importance.

Between-group differences for all three imputed quality-of-life measures are shown in Table 2, included unadjusted, baseline-score-adjusted and full-covariate-adjusted estimates.

Discussion

Patient-level data from the BLISTER trial provide the most robust evidence to date on whether tetracycline-initiated therapy is cost-effective as a treatment for patients with BP. The trial addresses the comparative short-term effectiveness and
long-term safety of doxycycline and prednisolone. In the base-case analysis (using multiple imputation), similar costs and outcomes were found regardless of whether patients received doxycycline-initiated therapy or prednisolone-initiated therapy. The joint distribution of costs and QALYs nonetheless suggests that doxycycline-initiated therapy may not be cost-effective. However, this finding seems to have been driven by the performance of the subgroup of patients with severe disease.

For patients presenting with mild or moderate disease, the economic and clinical findings align, and therefore treatment decisions for those with mild or moderate disease should be patient-led and informed by the different profiles of the two drugs. Conversely, the clinical and economic findings for patients with severe disease differ, and the economic analysis provides a clear preference for prednisolone-initiated therapy for patients presenting with severe disease. These findings were robust to a range of sensitivity analyses using the complete-case dataset, total rather than attributed costs, and different levels of model adjustment.

The profile of EQ-5D scores encompasses short-term and long-term patterns (Table S1). A small quality-of-life benefit for prednisolone may occur in the first few months but disappears by 6 months. Hence, although an extrapolation exercise was originally planned as part of the economic analysis, with modelling beyond 12 months, there was no rationale to pursue this in the absence of significant differences in quality of life or mortality.

This study has some limitations. BP is a rare disease affecting mainly the very elderly, and so recruitment to trials in this disease is a challenge. BLISTER recruited 253 patients from 54 U.K. and seven German hospitals over 4-5 years. The extent of blistering was a stratification variable within the trial randomization, making the strata subgroups into nested randomized controlled comparisons within the overall trial. Reflecting the subgroup patient numbers, differentiation of cost-effectiveness by extent of blistering would be strengthened by further evidence before prioritizing prednisolone routinely for patients with severe blistering.

BLISTER compared doxycycline-initiated with prednisolone-initiated treatment rather than being an explanatory trial evaluating the pharmacological effects of these treatments. It is possible that differences in cost and outcome may have been diluted by patients switching study drugs.

Economic analysis, by modelling the bivariate distribution of costs and QALYs, involves a range of assumptions. Judgements are made about the base-case model, the estimation method, adjustment for covariates, attribution of resource use and unit costs applied, as well as the quality-of-life measure used and societal weighting applied.

Incompleteness of the data contributing to the economic analysis is a further potential weakness, a consequence of trying to maintain data quality in a group of mainly elderly patients with multiple morbidities across a high number of recruiting sites and over a long period of time. Exploring the consequence of imputation, the findings appear robust within a range of sensitivity analyses. However, multiple imputations inevitably requires strong assumptions about data being missing at random, which are only partially testable. Careful consideration of modelling issues and use of sensitivity analyses, exploring assumptions, provide some indication of the robustness of the findings.

Patient-level data from the BLISTER trial provide the most robust cost-effectiveness evidence to date comparing doxycycline- and prednisolone-initiated treatment for patients with BP. It should be noted that both drugs are inexpensive and in routine use. The base-case analysis found similar, if imprecise, costs and outcomes regardless of whether patients received doxycycline-initiated therapy or prednisolone-initiated therapy. However, post hoc subgroup analysis of patients with severe blistering produced discrepant findings. On cost-effectiveness grounds, there is a clear preference for prednisolone-initiated therapy for those with severe disease. Discrepant findings might be further understood by further trial-based evidence, and also by qualitative work exploring patients’ views on the trade-off between short-term blister control and long-term safety.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

Table S1 Health status, resource use and cost (complete cases).

Table S2 Cost-effectiveness, cost per quality-adjusted life-year (£, 2013): doxycycline vs. prednisolone.