Is speed of healing a good predictor of eventual healing of pyoderma gangrenosum?

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Background: Pyoderma gangrenosum is a rare inflammatory skin condition. Two prospective studies have evaluated treatments for pyoderma gangrenosum using a primary outcome of healing speed at 6 weeks.

Objective: Using data from both studies we assessed the predictive value of 3 early predictors for healing at 6 months: speed of healing, Investigator Global Assessment (IGA), and resolution of inflammation, recorded at 2 and 6 weeks.

Methods: Logistic regression models were applied and the effectiveness of the 3 measures was assessed through estimating the positive and negative predictive values and the area under the receiver operating characteristic curve.

Results: The positive and negative predictive value at 6 weeks were, respectively, 63.5% (95% confidence interval [CI] 52.4%-73.7%) and 74.6% (95% CI 62.5%-84.5%) for speed of healing; 80% (95% CI 68.7%-88.6%) and 74.2% (95% CI 64.1%-82.7%) for IGA; and 72.1% (95% CI 59.9%-82.3%) and 68.1% (95% CI 57.7%-77.3%) for resolution of inflammation. IGA had the best combined positive predictive value, negative predictive value, and area under the receiver operating characteristic curve at 2 and 6 weeks.

Limitations: We were limited by data available from existing datasets.

Conclusion: Speed of healing, IGA, and resolution of inflammation were all shown to be good predictors of eventual healing of pyoderma gangrenosum. (J Am Acad Dermatol 2016;75:1216-20.)

Key words: clinical practice; clinical trials; lesion improvement; predictors; pyoderma gangrenosum; resolution of inflammation; speed of healing.

Pyoderma gangrenosum is a rare inflammatory skin condition that causes tissue to become necrotic, leaving deep ulcerative lesions. These ulcers can be painful, can rapidly spread, and may take many months to heal.[1] There is a paucity of evidence for pyoderma gangrenosum treatments.[2] Most evidence is based on observational studies and only 2 randomized controlled trials (RCTs) have been

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conducted to date.[1,3] One of the challenges of conducting research into rare skin conditions such as pyoderma gangrenous is the lack of validated outcome measures for assessing treatment response.

The primary outcome for 2 recently completed studies (STOP GAP RCT[3] and STOP GAP prospective cohort study[4]) was speed of healing over the first 6 weeks of treatment. Initial treatment response was used as a surrogate measure for time to healing, which is more clinically relevant in that it influences patient satisfaction, cumulative drug exposure, and drug safety.

Speed of healing, if valid, could become a useful surrogates for eventual healing and could be used to guide early treatment decisions in clinical practice.

Although speed of healing has been shown to be a good predictor of healing in patients with leg ulcers caused by venous disease,[5,6] it is unclear whether the same applies to patients with an inflammatory condition such as pyoderma gangrenosum.

Using data from the STOP GAP trial and cohort study, we investigated whether speed of healing in the first 6 weeks of treatment was a good indicator of subsequent healing in patients with pyoderma gangrenosum, or whether other measures, such as Investigator Global Assessment (IGA) for lesion improvement or resolution of inflammation were more useful.

CAPSULE SUMMARY

- Speed of healing has been shown to be a good predictor of eventual healing for leg ulcers.
- We found that speed of healing, Investigator Global Assessment, and resolution of inflammation are all good predictors of eventual healing for pyoderma gangrenosum.
- This finding is helpful for informing future trial design and clinical decision-making.

METHODS

This work involved secondary data from previous studies and as such did not require specific approval from an institutional review board.

Study conduct

Ethics and regulatory approvals were obtained for the STOP GAP trial and cohort studies (ethics: 09/H0903/5, Medicines and Healthcare Products Regulatory Agency: 19162/0213/001); all participants gave written informed consent. Oversight of the study was performed by independent Trial Steering Committee and Data Monitoring Committee. Specific ethical approval for this study was not required.

Summary of the STOP GAP trial and STOP GAP cohort study

Both the RCT and the cohort study included adults with a clinical diagnosis of pyoderma gangrenosum (as confirmed by a dermatologist, with biopsy as required), and followed up participants for a maximum of 6 months. For the STOP GAP trial, participants were randomized to receive either cyclosporine or prednisolone, and in the cohort study, participants received topical therapy according to local practice (49/74% received clobetasol propionate 0.05%).

For participants with multiple lesions, a target lesion was chosen for study. This was defined as being the largest lesion on a single plane (ie, not around the curvature of a limb). Lesions were measured by physical measurements taken by the clinician. Grade for lesion improvement was also measured by the clinician using an IGA and resolution of inflammation was measured using the scale reported by Foss et al.[7] Details of each of these scales are given in Supplementary Fig 1.

For patients participating in the RCT, lesion size, grade for lesion improvement (IGA), and resolution of inflammation were also assessed by an independent assessor using digital images. For lesion size the measurements were taken from the digital images using Verge Videometry computerized planimetry. An example of measurements being taken from a digital image is shown in Supplementary Fig 2. These measurements were used in the analyses of the primary and secondary outcomes in the RCT. Where digital images were not available or were of poor quality, the physical measurements recorded by the clinician were used instead. These physical measurements approximated lesion area through the formula: length $\times$ width $\times$ 0.785.

Outcomes were captured at baseline, 2 weeks, 6 weeks, and when the ulcer had healed (up to a maximum of 6 months). Lesions were considered to have healed when sterile dressings were no longer required as reported by patients. If this information was missing, then healing as confirmed by a clinician at the next clinic visit was used instead. Further details of the STOP GAP trial and cohort study are described elsewhere.[3,4]

Patient populations

The sample size for this study was based on available data. We analyzed data from 112 patients