BJD
British Journal of Dermatology

Systematic reviews of case reports and case series: from anecdote to evidence

DOI: 10.1111/bjd.16073

Linked Article: Song *et al.* Br J Dermatol 2018; **178**:363–368.

In this issue of the BJD, Song and colleagues systematically review the literature on the treatment of refractory pyoderma gangrenosum (PG) with intravenous immunoglobulin (IVIG).[1] Their manuscript demonstrates several challenges to studying IVIG for refractory PG, and rare diseases more broadly. It also demonstrates some of the challenges of systematically reviewing the literature for case reports, and highlights the role of case reports and case series within the context of epidemiological literature.

Firstly, PG is rare. Secondly, there is not a clear definition of refractory disease. Although ciclosporin has been identified as a 'first-line' agent for PG, there are limited data on the expected response, which contributes to the difficulty of defining refractory disease.[2] In fact, the majority of patients reported in this review were not previously treated with ciclosporin. Thirdly, PG is a clinically heterogeneous condition; the authors included all variants of PG in their review, including some that are likely mechanistically different from classic PG, like PAPA syndrome. Due to the small sample size, assessment of therapeutic effectiveness among variants is limited. Fourthly, tools for measuring PG response to therapy are lacking. While we can assume that complete response is defined by resolution of the ulcer and resolution of inflammation, our current measurement tools do not define partial response or provide guidance on how to assess response in the setting of multiple lesions. Lastly, because the majority of reported cases did not receive IVIG monotherapy, it is difficult to assess the true effectiveness of IVIG or recommend an appropriate multi-agent regimen for refractory PG.

This review also demonstrates challenges in summarizing therapeutic evidence for rare and heterogeneous conditions. Randomized controlled trials (RCTs) have not been performed for refractory PG; management of refractory PG has been examined only in case reports and case series. In the hierarchy of epidemiological evidence, case reports and case series are typically considered the lowest level of evidence, while RCTs and systematic reviews and meta-analyses of RCTs are at the top. Nonetheless, case studies and case series hold an important place in the medical literature, especially for hypothesis generation, recognition of sentinel events and studying outcomes of rare diseases or new treatments.[3,4] A new paradigm suggests that systematic reviews are a lens that can be helpful for appraising and synthesizing available data of all types, providing recognition of the inherent limitations of the data.[5] Despite a lack of 'high-quality' evidence, clinicians still have to make treatment decisions for patients with refractory PG. Reviews like that by Song *et al.*[1] can help guide decision making for rare diseases by summarizing the range of doses and time to outcomes previously experienced, even when the limited nature of the data prevent generation of summary statistics on efficacy.

Systematic reviews of case reports and case series require a number of important methodological considerations and, increasingly, tools are available to help improve the methodological quality. Firstly, standardized reporting of case reports facilitate their synthesis, and reporting guidelines have been developed specifically for this purpose.[6] Secondly, critical appraisal of the quality of included reports is essential, and quality assessment tools are available to facilitate this process.[7] A common limitation in systematic reviews is publication bias. This may be particularly problematic and difficult to measure among case reports because investigators are unlikely to report interventions that do not work, and registries analogous to www.clinicaltrials.gov, which may include unpublished reports, do not exist. Consecutive case series or retrospective cohort studies can help to address this issue, but are subject to other limitations including reduced generalizability. A related challenge is that traditional databases such as PubMed/MEDLINE, EMBASE and Web of Science may not include all published case reports, especially those that are not peer reviewed. Increasingly, there are journals dedicated exclusively to case reports, and there have been efforts to develop a comprehensive database of case reports.[8] Once such a database is available, it should be included in the search strategy for all systematic reviews of case studies.

In conclusion, there are a number of challenges to research on rare and heterogeneous conditions. Case reports and case series fill an important role as the initial data source for such conditions, and when carefully performed, systematic reviews of case reports and case series can provide a useful addition to evidence-based medicine.

Acknowledgments

The authors would like to thank Tim Berger for his comments on a draft of this commentary.

Conflicts of interest

None to declare.

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References

1 Song H, Lahood N, Mostaghimi A. Intravenous immunoglobulin as adjunct therapy for refractory pyoderma gangrenosum: systematic review of cases and case series. *Br J Dermatol* 2018; **178**:363–68.
2 Reichrath J, Bens G, Bonowitz A, Tilgen W. Treatment recommendations for pyoderma gangrenosum: an evidence-based review of the literature based on more than 350 patients. *J Am Acad Dermatol* 2005; **53**:273–83.
3 Kempen JH. Appropriate use and reporting of uncontrolled case series in the medical literature. *Am J Ophthalmol* 2011; **151**:7–10 e11.
4 Vandenbroucke JP. In defense of case reports and case series. *Ann Intern Med* 2001; **134**:330–4.
5 Murad MH, Asi N, Alsawas M, Alahdab F. New evidence pyramid. *Evid Based Med* 2016; **21**:125–7.
6 Gagnier JJ, Kienle G, Altman DG *et al.*; CARE Group. The CARE guidelines: consensus-based clinical case reporting guideline development. *BMJ Case Rep* 2013; **2013**: pii: bcr2013201554.
7 Moga C, Guo B, Schopflocher D, Harstall C. *Development of a Quality Appraisal Tool for Case Series Studies Using a Modified Delphi Technique*. Edmonton (AB): Institute of Health Economics, 2012.
8 Ketterman E. Cases database. *J Med Libr Assoc* 2014; **102**:137–8.

What can we learn from 'dropouts' in clinical trials?

DOI: 10.1111/bjd.16220

Linked Article: Nast *et al.* Br J Dermatol 2018; **178**:400–405.

In this issue of the *BJD*, Nast *et al.* analyse the reasons for participants with psoriasis dropping out of randomized clinical trials (RCTs) for etanercept.[1] Before discussing their findings, we must first put this study into context. RCTs are a necessary step between the preclinical evaluation of pharmaceuticals and their use and assessment in the real world. However, RCTs create an artificial situation that can be quite remote from the real world.[2] This starts with the selection of the study subjects, who may well differ from most persons seen in clinical practice with respect to concomitant diseases and medications, as well as in compliance and sex, age and socioeconomic characteristics.[3–5] As an RCT attempts to show the drug's efficacy, which means the maximal effect of a drug under ideal circumstances, the sponsor tends to select participants that are most likely to be associated with a favourable outcome. This has led to a discussion about the integrity of RCTs.[6,7] All this leads to a high internal, but low external validity of RCTs. This means that the findings of an RCT are true within the borders of a given RCT, but cannot be generalized to the different and more complex real-world situation. To extract knowledge from dropouts in clinical trials that is relevant in the real world is a particularly delicate issue, given the chronic nature of psoriasis compared with the short duration of RCTs.

Nast *et al.* investigated only dropouts under a single drug, etanercept, by pooling data from 10 RCTs. Of 6119 participants included, 128 (2·1%) dropped out due to lack of efficacy. This surprising low frequency of dropouts – given the relatively low percentage of participants who do achieve Psoriasis Area and Severity Index (PASI) 75 – points towards the fact that not all participants with a disappointing efficacy are visible here. The frequent contact with the caregiver within clinical trials might have influenced dropout frequency and reasoning. Participants may prefer other arguments for discontinuing which they perceive as more acceptable; or might even continue – although there is lack of efficacy – until near the end of the trial before they give up. Actually, such a pattern was described by Nast *et al.*;[1] dropouts peaked at around day 80 – and several of the included trials had a (blinded) length of 84 days.

However, this study supports an interesting observation that many of us have observed in clinical practice: persons with less severe psoriasis measured by PASI at baseline are harder to improve sufficiently and less likely to adhere to therapy compared with those with more severe psoriasis at baseline. Conversely, those with higher PASI scores might be more likely to find their disease improved. Furthermore, dropouts experienced their skin-related quality of life to be more negative than those who continued in the study. The averaged PASI and Dermatology Life Quality Index (DLQI) at baseline were: continuers (dropouts) PASI 16·5 (10·8) and DLQI 12·0 (19·5). This means that dropouts tended to report a higher DLQI although they had a lower PASI. It is up to future research requiring a holistic view on persons with psoriasis to analyse how this differing disposition of the dropouts – to experience their skin-related quality of life more negatively – can be overcome.

Acknowledgments

The author would like to thank Robert S. Stern for his critical revision of this commentary.

Conflicts of interest

Dr Schmitt-Egenolf is responsible for Dermatology in the project management for the National Guidelines for Psoriasis at the Swedish Board of Health and Welfare.

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References

1 Nast A, Dilleen M, Liyanage W *et al.* Time, Psoriasis Area and Severity Index and Dermatology Life Quality Index of patients with psoriasis who drop out of clinical trials on etanercept because of lack of efficacy: a pooled analysis from 10 clinical trials. *Br J Dermatol* 2018; **178**:400–5.
2 Schmitt-Egenolf M. Psoriasis therapy in real life: the need for registries. *Dermatology* 2006; **213**:327–30.

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