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Response to ‘Kidney disease in moderate-to-severe psoriasis: a critical appraisal’

J. Wan and J.M. Gelfand

Department of Dermatology and the Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, U.S.A.

We appreciate the critical appraisal that Jabbar-Lopez et al. have performed on our article published in the BMJ.¹ The authors have done a very nice job of highlighting the strengths of the study, as well as some important issues for further discussion. We thank them for featuring our study in the BJD, and we appreciate the opportunity to present our comments in response.

Limitations in primary care medical records databases

We agree with the authors’ point that, generally, there may be inherent limitations to using medical records databases for epidemiological studies. With respect to our study, they note that the use of The Health Improvement Network (THIN) database biases towards selecting patients with psoriasis who are managed in primary care. However, our group has previously published on the validity of our approach and shown how specialist data are captured in THIN.² In our Incident Health Outcomes and Psoriasis Events cohort, we also asked general practitioners (GPs) whether patients had been seen by a dermatologist and found that 46% of patients with psoriasis had had their diagnosis corroborated by a dermatologist. Moreover, the capture of treatments such as methotrexate and phototherapy appears to be in line with expected utilization of these modalities in a population-based cohort of patients with psoriasis.³ Therefore, THIN captures not only patients who have mild psoriasis followed in primary care, but also those with more severe disease requiring specialist care.

Related to this discussion is the authors’ comment that systemic medications, including biological drugs, are poorly captured in THIN as many are only prescribed by specialists. In THIN, the GP is responsible for entering communication from specialists into the patient’s medical record. We would expect that conditions newly diagnosed by specialists, as well as ongoing treatments prescribed by specialists, particularly systemic or higher-risk medications, are noted by GPs in the medical record as they affect the overall medical care of the patient. As psoriasis is a chronic condition usually requiring long-term treatment in the outpatient setting, the concern that inpatient drugs prescribed by hospital doctors will be missed in THIN is less relevant. While it is possible, owing to incomplete documentation in THIN, that the rate of biologics use was low in our study cohort, the use of biological drugs

Correspondence: J.M. Gelfand. joel.gelfand@uphs.upenn.edu.

Conflicts of interest

J. Wan has nothing to disclose.

for psoriasis was also less common during the time of our study (2003–10) than now. The British Association of Dermatologists first published guidelines on biologics use for psoriasis in 2005,⁴ and even by 2009 the use of biological therapy remained limited in the U.K., owing to shortfalls in funding.⁵

Nevertheless, we agree with the authors that primary care data may not completely capture all diagnoses and therapies given in secondary care. To the extent that incomplete data are related to the outcome of interest, unmeasured confounding and/or misclassification bias can be introduced. In the case of kidney disease outcomes, ciclosporin would be the main concern for this error; however, its use was captured in our study, and the drug is not commonly used, making it unlikely to explain the association observed between psoriasis and chronic kidney disease (CKD).

Information bias

The authors mention that ascertainment bias may have arisen from national laboratory reporting and policy changes during the period of our study. Although enhanced case finding and increased coding of CKD by GPs may have influenced the incidence measures of CKD in our study, such national-level changes would presumably minimize differential ascertainment between patients with psoriasis and those without psoriasis, as the patients without psoriasis are now also subject to closer screening and reporting of estimated glomerular filtration rate abnormalities. We agree that it is important to test for ascertainment bias and thus we conducted a series of sensitivity analyses to ensure all patients were actively followed and screened for kidney disease (which did not alter our primary findings). Furthermore, our results extended to end-stage renal disease (ESRD) requiring dialysis, a hard end point that is not likely to be affected by ascertainment bias.

Confounding

In our study, we considered many potential confounders, including the use of possibly nephrotoxic medications. The authors point out that while we performed sensitivity analyses excluding patients on azathioprine monotherapy or ciclosporin and/or methotrexate mono-/combination therapy, we did not exclude patients receiving tacrolimus or mycophenolate, raising the concern that this may lead to an overestimation of the results. We believe an overestimation is unlikely as tacrolimus and mycophenolate were rarely used for psoriasis (both used in 1% of the patients in our cohort) and thus would not meaningfully alter the estimates. We also excluded all patients with prevalent CKD at the beginning of the study, so if patients had been taking medications such as tacrolimus or mycophenolate in the setting of renal transplantation, as suggested by the authors, we excluded them from the cohort.

External validity

The use of a population-based cohort design is expected to enhance the generalizability (external validity) of the results. In the time since our study was published, a few other papers have also reported an increased risk of CKD and ESRD among patients with severe

psoriasis,^{6,7} and an increased risk of death from renal disease among patients with psoriasis.⁸

Implications of the study findings and future directions

A single observational study rarely proves causality on its own; however, we are intrigued by the dose–response relationship observed between psoriasis severity and CKD, which may be suggestive of possible causality and warrant closer examination in future studies.

The implications of our findings on clinical practice are yet to be fully determined, and the authors raise many good discussion points. The possible overdiagnosis of mild-to-moderate CKD that may never progress to symptomatic disease is an interesting question in its own right. Even so, our study found an increased risk of ESRD and/or haemodialysis dependence among patients with severe psoriasis, and other studies have demonstrated an increased risk of renal-related mortality, suggesting that patients with more severe psoriasis may benefit from changes in clinical practice. Closer monitoring for renal insufficiency, such as routine screening urinalysis for microalbuminuria and serum creatinine and blood urea nitrogen testing, should be considered for patients with psoriasis affecting 3% of the body surface area. Moreover, adequate treatment of risk factors for CKD, such as hypertension, is essential in patients with psoriasis.⁹ Additionally, the risk vs. benefit of using potentially nephrotoxic drugs in patients with moderate-to-severe psoriasis should be carefully considered. Future research is needed to confirm and expand our findings, to delineate the biological mechanisms underlying renal disease in psoriasis and to further examine the impact of psoriasis treatments on the risk of CKD.

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References

1. Wan J, Wang S, Haynes K, et al. Risk of moderate to advanced kidney disease in patients with psoriasis: population based cohort study. *BMJ*. 2013; 347:f5961. [PubMed: 24129480]
2. Seminara NM, Abuabara K, Shin DB, et al. Validity of The Health Improvement Network (THIN) for the study of psoriasis. *Br J Dermatol*. 2011; 164:602–609. [PubMed: 21073449]
3. Nevitt GJ, Hutchinson PE. Psoriasis in the community: prevalence, severity and patients' beliefs and attitudes towards the disease. *Br J Dermatol*. 1996; 135:533–537. [PubMed: 8915141]
4. Smith CH, Anstey AV, Barker JN, et al. British Association of Dermatologists guidelines for use of biological interventions in psoriasis 2005. *Br J Dermatol*. 2005; 153:486–497. [PubMed: 16120132]
5. Smith CH, Anstey AV, Barker JN, et al. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. *Br J Dermatol*. 2009; 161:987–1019. [PubMed: 19857207]

6. Chiu HY, Huang HL, Li CH, et al. Increased risk of glomerulonephritis and chronic kidney disease in relation to the severity of psoriasis, concomitant medication, and comorbidity: a nationwide population-based cohort study. *Br J Dermatol*. 2015; 173:146–154. [PubMed: 25511692]
7. Chi CC, Wang J, Chen YF, et al. Risk of incident chronic kidney disease and end-stage renal disease in patients with psoriasis: a nationwide population-based cohort study. *J Dermatol Sci*. 2015; 78:232–238. [PubMed: 25862150]
8. Svedbom A, Dalen J, Mamolo C, et al. Increased cause-specific mortality in patients with mild and severe psoriasis: a population-based Swedish Register study. *Acta Derm Venereol*. 2015; 95:809–815. [PubMed: 25766866]
9. Takeshita J, Wang S, Shin DB, et al. Effect of psoriasis severity on hypertension control: a population-based study in the United Kingdom. *JAMA Dermatol*. 2015; 151:161–169. [PubMed: 25322196]