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Systemic antipsoriatic treatment: do women respond better than men and if so, why?

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Reports on antipsoriatic treatment responses specifically evaluating sex differences are scarce. Maul *et al.*[1] undertook a major effort and now report from a two-country study on data of more than 5300 patients with moderate-to-severe psoriasis extracted from psoriasis registries of Germany (PsoBest) and Switzerland (SDNTT). These registries are fed by data from 880 office-based dermatology practices and academic or hospital-based outpatient clinics in Germany and eight academic dermatology departments in Switzerland. The investigators report slight but statistically significant better response rates throughout the 12-month observation period of the study in women compared with men, who started their treatments with slightly higher Psoriasis Area and Severity Index (PASI) score. After 12 months, 72·3% of women vs. 66·1 of men not only reached PASI75 reduction or an absolute PASI of ≤ 3 but also in parallel, a significantly higher proportion of women experienced a better quality of life during the observation period, measured by improvement of the Dermatological Quality of Life Index (DLQI) score of ≥ 4 in 70·7% of women vs. 64·4% men. Of importance to note, the range of percentages of women and men (40·4% vs. 59·6%) in this analysis were similar to that in other registry reports.[2,3] However, at treatment baseline, women not only had a lower PASI score than men (13·1 vs. 14·9), consistent with previous work,[4] but also were slightly older (48·3 vs. 47·1 years) and had less body weight (77·5 vs. 90·9 kg), although their body mass index was nearly identical (28·2 vs. 28·5 kg m^{-2}). With regard to treatment allocation, the majority of patients (71·6% of women and 69·4% of men) in this two-country analysis had received nonbiologic agents, i.e. mainly fumaric acid esters and methotrexate although the latter drug was administered less often in women than in men (4·4% vs. 15·8%). The biologics administered to the remaining smaller portion (around 30%) of patients included etanercept, infliximab, adalimumab, ustekinumab and secukinumab.

Going beyond hormonal status, how could these differences in treatment response between women and men be explained, even if, as pointed out by the investigators, the lower weight of women compared with men, and based on sex- and weight-independent standard dosing, a relatively higher dosing of drugs in women could have contributed to improved effectiveness? Alternatively, or additionally, different patient needs[5] and/or a better drug adherence might have contributed to a better outcome, comparing women and men. Intriguingly, however, previous studies have indicated that female sex was associated with an increased risk of stopping biologic treatment, including tumour necrosis factor antagonists, ustekinumab and anti-interleukin (IL)-17 antibodies,[2,3,6–8] as revealed by drug-survival analysis, a concept coined for treatment outcome in psoriasis by Gniadecki and colleagues.[6,9,10] However, drug survival does not only incorporate drug effectiveness but also safety, reimbursement, availability of alternative treatment options and expectations of physicians and patients. Moreover, previous work has revealed that drug survival correlated directly with clinical effectiveness for certain drugs such as adalimumab and etanercept.[2] How this can be reconciled with the observed higher response rates in women compared with men needs to be addressed in future studies. Furthermore, as the two-country analysis by Maul *et al.*[1] was predominated in terms of numbers by patients treated with fumaric acid esters and methotrexate, future studies with real-life data will have to address whether the observed better response rates in women also hold in general for biologics, and in particular for the latest generation, i.e. anti-IL-17 or IL-23p19 antibodies.

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Epidemiology, comorbidities and mortality of pyoderma gangrenosum: new insights

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Pyoderma gangrenosum (PG) has a severe impact on patients and their quality of life. It is challenging to treat, and response to therapy is frequently disappointing. It carries significant morbidity and is associated with increased mortality.[1] Through anecdotal evidence, limited case series and a previous population-based study, numerous well-known underlying conditions predispose to, or are associated with, PG in about 50% of cases, demanding that clinicians need to always consider which, if any, of these are present and to treat the underlying condition that may be pathogenically driving the underlying inflammatory process. Newer insights point to the genetic association of PG with autoinflammatory syndromes, including hidradenitis and acne, due to abnormalities in PSTPIP1.[2]

The Nordic countries have a long tradition of registries for their national health services and were the first to establish lifelong registration of all citizens' health data. One such database is the Danish National Patient registry.[3] With a long track record, the registry has captured and coded all hospital attendances for all its population of around 5 million since 1977, but it has only reliably coded PG since 1994.

In this issue of the *BJD*, Ben Abdallah *et al.* report a nested case–control study of registrants with a primary diagnosis of PG with 10 matched controls for each case to increase statistical power and the robustness of estimates.[4] Including 1604 patients with PG, it is the largest study of its kind and gives insight into the odds of comorbidities being present at the time of first diagnosis, and subsequent risks for disease associations and mortality in this cohort vs. people without PG. This study confirms possible disease associations that we already recognize and provides insight into some that have not previously been recognized.

Unfortunately, as discussed by the authors, some data like smoking history, body mass index and treatment are not captured in Danish registries to facilitate more detailed analysis. Also, rather than being strictly a case–control study, the methodology of the observational study is complex, comprising a historical cohort design to follow up the risk of death and developing comorbidities in those with PG vs. those without, and a cross-sectional approach to the assessment of the prevalence of comorbidities at the index date.[5] For some of the prior associations, it is not clear if some might relate to PG treatment before presenting to hospital services (e.g. osteoporosis and peptic ulcer disease). It would also be good to know more about the rationale used for selecting what comorbidities to adjust for.

PG might arise as a cutaneous manifestation of systemic inflammation or might, of itself, contribute to chronic inflammation that can promote metabolic syndrome and the incidence of cardiovascular disease. While the unadjusted prevalence of cardiovascular disease was associated with PG, this was attenuated on adjustment for other comorbidities. The authors postulate that this dependent association (rather than independent) may represent the inclusion of intermediate variables rather than confounders in their model, whereby a pathway of related comorbidities such as haematological disease, inflammatory bowel disease, diabetes and others are involved in shaping the patient's overall comorbidity.

This study confirms previous work in predicting a threefold increase in mortality (hazard ratio 2·8 after adjustment). Overall, patients with PG had about twice the number of comorbidities than controls at diagnosis, with cerebrovascular disease, chronic pulmonary disease, heart failure, cardiomyopathy, mild liver disease, myocardial infarction, osteoporosis, hemi-/paraplegia peripheral vascular disease and peptic ulcer being reported as new associations. Acne and hidradenitis stand out to dermatologists, with a fourfold increase in odds for PG in those with these conditions at the index date, which may point to underlying similarities in