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Comment on: "Effect of intravenous immunoglobulin on infections in multiple myeloma patients receiving daratumumab"

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We read with great interest the article by Lancman et al. investigating intravenous immunoglobulin (IVIG) replacement therapy and infection rates in patients with multiple myeloma (MM) receiving daratumumab [1]. The authors provide clinically relevant evidence showing that IVIG exposure was associated with a 43% reduction in all-grade infections and a 70% reduction in grade 3–4 infections compared with observation periods. These findings raise an important question for clinical practice: how should infection history and immune impairment be integrated to identify patients most likely to benefit from replacement?

These findings address an increasingly important issue in MM management. Infection prevention requires consideration of disease-related, treatment-related and patient-related factors, with immunoglobulin replacement reserved for selected clinical circumstances [2]. The study by Lancman et al. contributes valuable evidence to this approach, while highlighting the need to refine patient selection.

Several aspects deserve particular consideration.

First, the association between the severity of hypogammaglobulinaemia and infection rates confirms the relevance of immunoglobulin levels to risk assessment. Patients selected for IVIG also had a greater burden of infections before daratumumab initiation than those in the untreated reference cohort. These observations support considering laboratory findings and infection history together, rather than assigning priority to either in isolation. However, identifying a higher risk of infection does not necessarily establish which patients benefit most from replacement. A higher baseline risk may yield a greater absolute benefit even if the relative treatment effect is similar; whether either characteristic modifies that effect remains unresolved. This distinction is relevant when translating an observed association into practical criteria for IVIG initiation.

Second, the self-controlled case series design represents an important methodological strength, as each patient serves as their own control, reducing the influence of time-invariant confounding factors. The authors also addressed pre-exposure infection risk, disease progression and seasonality in additional analyses, with persistence of the protective association. These analyses strengthen the findings. Nevertheless, changes in concomitant treatment, corticosteroid exposure and supportive care may still have influenced infection rates. The increase in infections during the 60 days preceding IVIG initiation is consistent with infection-driven prescribing and underscores the selected nature of the treated population. Similarly, the untreated reference cohort provides useful context regarding patient selection but should not be interpreted as a comparable control group for estimating IVIG efficacy.

Third, the finding that severe lymphopenia was present during nearly half of grade 3–4 infectious episodes in the IVIG cohort deserves further attention. This observation reinforces the concept that susceptibility to infection is multifactorial and cannot be explained solely by hypogammaglobulinaemia. However, lymphocyte counts obtained during infection do not establish whether lymphopenia preceded the event or predicts benefit from replacement. Longitudinal assessment could help distinguish persistent immune impairment from changes accompanying an acute infection. More broadly, evaluation of secondary hypogammaglobulinaemia should integrate clinical infections with quantitative and, where appropriate, functional assessment of humoral immunity [3]. In this context, subtracting the monoclonal component from total IgG estimates non-monoclonal IgG but does not directly measure antibody function.

An additional consideration concerns applicability to frontline treatment. The population studied by Lancman et al. was predominantly treated in the relapsed/refractory setting, with a median of two previous lines. The multicentre Italian experience reported by Rago et al. provides a complementary perspective: 148 of 472 patients receiving daratumumab-containing first-line regimens experienced infectious complications [4]. This finding highlights the importance of infection prevention from the earliest stages of treatment, without establishing the efficacy of IVIG in this setting. Newly diagnosed patients may have clinically relevant immune impairment but a limited documented infection history. Requiring recurrent infections as the principal selection criterion could therefore delay recognition of some vulnerable patients; conversely, hypogammaglobulinaemia alone may lead to unnecessary replacement. How best to balance these considerations warrants prospective investigation.

To help inform this balance, it would be valuable to know whether the available data permit an exploratory description of absolute severe-infection rates during IVIG and observation periods according to preceding infection history and pre-replacement IgG levels. Given the small cohort, such findings would be hypothesis-generating, but could help define clinically relevant groups for prospective evaluation.

Prospective studies should incorporate standardised criteria for starting and discontinuing replacement, longitudinal immune monitoring, and outcomes such as serious infections, hospitalisation and treatment interruptions. Separate evaluation of newly diagnosed and previously treated patients would help establish whether the same selection criteria are appropriate across treatment settings.

In conclusion, Lancman et al. provide encouraging evidence supporting IVIG replacement in selected daratumumab-treated patients. Their findings favour an integrated assessment of infection history and immune impairment, while leaving the optimal selection strategy open. Defining when replacement offers sufficient clinical benefit, particularly before recurrent infections have accumulated in frontline treatment, would be an important step towards a personalised approach that reduces infectious complications while avoiding unnecessary exposure, toxicity and healthcare costs.

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