

Baseline immunoparesis does not impact clinical outcomes in patients with newly diagnosed Waldenström Macroglobulinemia

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Introduction: Immunoparesis is increasingly recognized as a dynamic, prognostic marker of systemic immune dysregulation. While often related to increased tumor burden, its direct impact on clinical outcomes in Waldenström Macroglobulinemia (WM) remains underexplored.

Methods: We analyzed consecutive, newly diagnosed patients who initiated treatment since January 1, 2002. Baseline IgG levels were defined as: severe immunoparesis (<400 mg/dL), moderate (400-600 mg/dL), and normal (>600 mg/dL). Baseline IgA levels were classified as low (<70 mg/dL) or normal (≥70 mg/dL).

Results: 553 patients were evaluated. Baseline IgG levels were normal in 375 (67.8%) and decreased in 178 (32.2%) patients (120 [21.7%] moderate; 58 [10.5%] severe). IgA was low in 232 (42.0%) and normal in 321 (58.0%). No significant difference in frontline treatment selection was observed between the different IgG cohorts ($p = 0.699$).

At diagnosis, moderate/severe IgG suppression was strongly associated with higher IgM levels (median 4820 vs. 2912 mg/dL, $p < 0.001$). Patients with moderate/severe IgG immunoparesis had lower albumin levels (median 3.5 vs. 3.8 g/dL, $p < 0.001$) and more frequent concurrent IgA suppression (73.0% vs. 27.2%, $p < 0.001$). No significant differences were observed regarding age ($p = 0.206$), MYD88 L265P ($p = 0.310$) or CXCR4 ($p = 0.549$) mutations, bone marrow infiltration ($p = 0.324$), or R-IPSSWM risk group distribution ($p = 0.308$).

Immunoparesis did not seem to compromise treatment efficacy. Major response rates (defined as PR or better) were similar between the normal and moderate/severe IgG groups (58.1% vs. 59.6%, $p = 0.823$; 62.5% for moderate and 53.4% for severe, $p = 0.492$) and identical across IgA levels (58.6% vs. 58.6%, $p = 1.000$). In a multivariable regression model adjusting for baseline imbalances (albumin, IgA, gender, and IgM), IgG levels did not predict major response ($p = 0.403$), while treatment type (BTK inhibitors: OR 3.69, $p < 0.001$; chemoimmunotherapy: OR 2.32, $p < 0.001$) remained the primary driver.

Over a median follow-up of 8.49 years (95% CI: 7.88–9.38), survival analyses revealed no significant differences in PFS or OS with regards to immunoparesis (IgG: $p = 0.344$; IgA: $p = 0.842$) (IgG: $p = 0.505$; IgA: $p = 0.879$). For the moderate/severe IgG vs. normal cohorts, the 5-year OS was 77.3% vs. 75.0%, and the 10-year OS was 54.3% vs. 52.4%. For the low vs. normal IgA cohorts, the 5-year OS was 75.5% vs. 75.7%, and the 10-year OS was 51.1% vs. 54.4%.

The cumulative incidence of WM-related mortality was comparable regardless of IgG immunoparesis ($p = 0.50$), IgG levels ($p = 0.49$), or low IgA levels ($p = 0.62$). For the moderate/severe IgG vs. normal cohorts, the 5-year cumulative incidence of WM-related mortality was 14.5% vs. 12.2%, and the 10-year cumulative incidence was 23.3% vs. 22.5%. For the low vs. normal IgA cohorts, the 5-year cumulative incidence of WM-related mortality was 13.5% vs. 12.6%, and the 10-year cumulative incidence was 23.5% vs. 22.4%.

Conclusion: In NDWM patients baseline immunoparesis is associated with higher IGM levels and hypoalbuminemia, however, does not seem to represent an adverse prognostic factor, having no impact on treatment response, PFS, OS, or disease-specific mortality

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