Comparison of short term outcomes and Safety profiles between daratumumab based quadruplet versus triplet induction regimen for Patients with transplant eligible new diagnosed Multiple Myeloma: Meta-analysis of randomized controlled trials

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INTRODUCTION

Multiple myeloma (MM) is a clonal plasma cell malignancy characterized by progressive infiltration of the bone marrow together with immune dysregulation [1]. Within the past ten years, there is a significant advancement in the treatment of multiple myeloma, especially the transplant-eligible newly diagnosed multiple myeloma (TE-NDMM). A standard induction therapy regimen is made up of Lenalidomide, Bortezomib, and Dexamethasone (RVd) as a triplet therapy [2]. Recently in clinical trials, GRIFFIN and PERSEUS have explored adding daratumumab (D), a CD38 monoclonal antibody, to this backbone, creating a quadruplet regimen (D RVd), which showed great results both in efficacy and disease response [3]. Although some studies with single participants showed benefit, a review based on combining the results of the randomized controlled trial (RCT) had not been done. We present a metanalysis that evaluated the short-term efficacy of D-RVd, in comparison with RVd, in terms of clinical outcomes as well as safety, in patients with TE-NDMM.

METHODS

We conducted a meta-analysis of RCTs from inception to May 8, 2025. The search of the electronic databases such as PubMed, Embase, and Cochrane Central was not limited by language. Our inclusion criteria was limited to: randomized controlled trials; patients with transplant-eligible, newly diagnosed multiple myeloma (TE-NDMM); comparisons of D-RVd (Daratumumab + RVd) vs RVd alone; reported outcomes on efficacy and/or safety. The outcomes assessed Included: stringent complete response (sCR) at the end of post-autologous stem cell transplant (ASCT) consolidation; minimal residual disease (MRD) negativity at 10^{-5} sensitivity by next-generation sequencing. Our safety criteria included: overall mortality; any grade neutropenia; any grade infection. Our statistical analysis incorporated a random-effects model measure of pooled risk ratio (RR) and 95% confidence interval (CI) was calculated on binary outcomes. Analyses were done using mean differences (MD) in case of continuous variables. The statistic was used to measure the heterogeneity among the studies; above 50% shows that a study was not highly homogeneous.

RESULTS

A total of six RCTs were included, encompassing 2520 patients: 1283 in the D-RVd group and 1237 in the RVd group.

Efficacy Findings:

Stringent Complete Response (sCR):

Patients treated with D-RVd achieved significantly higher sCR rates compared to RVd (38% vs 28.99%).

- RR: **1.25 (95% CI: 1.11–1.41)**
- p = 0.0003, I² = 0%(Figure 1A)
- *Interpretation*: The addition of daratumumab improves deep remission rates with low heterogeneity across studies.

RESULTS (CONTINUED)

- **MRD Negativity (10^{-5}):**

  D-RVd significantly improved MRD-negativity rates compared to RVd.
  - RR: **1.77 (95% CI: 1.46–2.14)**
  - p < 0.00001, I² = 65%(Figure 1B)
  - *Interpretation*: The quadruplet regimen leads to deeper molecular responses, although heterogeneity was moderate.

Safety Outcomes:

- **Overall Mortality:**

  Patients receiving D-RVd had a lower mortality rate compared to those on RVd.
  - RR: **0.64 (95% CI: 0.46–0.90)**
  - p = 0.001, I² = 0% (Figure 1C)
  - *Interpretation*: The addition of daratumumab does not increase short-term mortality risk and may offer a survival benefit.
- **Neutropenia (any grade):**

  A higher rate of neutropenia was observed with D-RVd.
  - RR: **1.62 (95% CI: 1.25–2.11)**
  - p = 0.0003, I² = 67%(Figure 1D)
  - *Interpretation*: Hematologic toxicity, especially neutropenia, is more pronounced with the quadruplet regimen.
- **Infections (e.g., pneumonia):**

  There was no statistically significant difference between groups.
  - RR: **1.22 (95% CI: 0.85–1.77)**
  - p = 0.29, I² = 33%(Figure 1E)
  - *Interpretation*: Infection risk remains comparable, though close monitoring is advised.

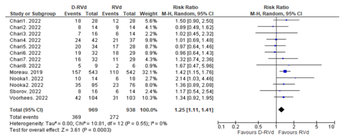


Figure 1A: Comparison of stringent complete response (sCR) between the groups

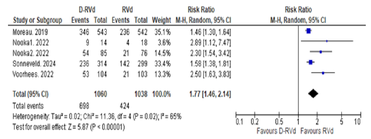


Figure 1B: Comparison of MRD-negativity (10-5) between the groups

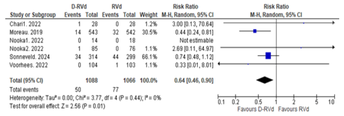


Figure 1C: Comparison of overall mortality between the groups

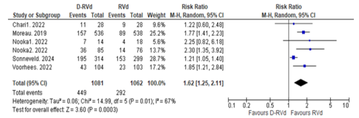


Figure 1D: Comparison of neutropenia between the groups

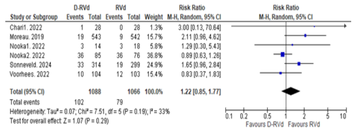


Figure 1E: Comparison of infection (Pneumonia) rates between the groups

DISCUSSION

This meta-analysis using six randomized controlled trails emphasizes the clinical advantage of including daratumumab to RVd backbone in multiple myeloma transplant-eligible and newly diagnosed (TE-NDMM). As compared to RVd, short-term efficacy was significantly higher in D-RVd across rates of stringent complete response (sCR) and minimal residual disease (MRD)-negative rates at a 10^{-5} sensitivity.

The 25 percent relative rise in sCR as well as 77 percent relative rise in MRD-negativity shows the level of response depth acquired with the administration of daratumumab-based quadruplet therapy. MRD negativity, which is a surrogate marker to progression-free and overall survival, supports the intensity of response of D-RVd [4,5].

From a safety standpoint, our results are also reassuring. Although the likelihood of developing neutropenia was higher in patients with D-RVd, the increase was not significant in the rate of infections e.g. pneumonia. This is an indication that this extra hematologic toxicity of daratumumab can be easily managed, especially with multidisciplinary approach. Also, the safety of D-RVd is evidenced by the mortality benefit at the end of the intervention of D-RVd (RR 0.64), and potential short-term efficacy benefits are evidenced by the mortality benefit at the end of the intervention of D-RVd (RR 0.64), even at the relatively short follow-up periods reported in the included trials [3].

Our analysis is strengthened by its exclusive inclusion of RCT-level data, providing a robust evidence base. However, heterogeneity in MRD assessment methods and follow-up durations must be acknowledged. In conclusion, D-RVd should be considered a preferred induction approach in TE-NDMM, balancing superior response depth with an acceptable safety profile.

CONCLUSIONS

The results of the current meta-analysis of six RCTs conducted on the population of more than 2500 patients give substantial evidence in favor of using D- RVd as an induction therapy with transplant-eligible patients with NDMMs. These data support the value of the addition of daratumumab to standard induction immunochemotherapy, which provides deeper response and also a potentially better early survival profile.

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