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508.BONE MARROW FAILURE: ACQUIRED

Real-Life Data of Cyclosporine (CsA) Tapering in Patients with Very/ Severe Aplastic Anemia (v/sAA) Treated with Horse Anti-Thymocyte Globulin (hATG/CsA) Suggest Higher Risk of AA Relapse at Cyclosporine Plasma Levels below 100 Nanogram per Milliliter

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Introduction: Aplastic anemia (AA) is an acquired bone marrow failure syndrome (BMFS) mediated by autoreactive T-cells. In adults with severe (s) or very severe (vs) AA >40-50 years or ineligible for transplant for other reasons immunosuppressive therapy (IST) with anti-thymocyte globulin (ATG), cyclosporine A (CsA) and Eltrombopag (Epag) has recently become the actual standard of care. With CsA treatment maintained for 6 to 24 months followed by CsA tapering hematologic response is achieved in 60-70 % of AA patients (pts.), while 30-40 % are primary refractory. Approximately 40% of pts. relapse during CsA tapering and most relapsed AA pts. remain CsA dependent. In vitro data indicate a dose dependent inhibition of T cell activity induced by CsA, suggesting the presence of a therapeutic CsA threshold around 100 ng/mL (Flores et al. Front Immunol 2019). Pts. with CsA related side effects such as renal insufficiency would benefit from an established lowest efficient CsA plasma level preventing relapse and reducing CsA related toxicity. As data about correlation of CsA plasma levels and the occurrence of relapse during tapering are sparse, we analyzed data from our registries including CsA plasma levels of 20 s/vsAA pts. with and without relapse during CsA tapering after treatment with horse ATG/CsA.
Methods: Descriptive retrospective analysis of 20 AA pts. (17 sAA/ 3 vsAA) from the AA-BMF/Basel AA registry treated with horse ATG/CsA and sufficient clinical data during CsA tapering. Results are given as mean ± standard deviation. Mean age of the 13 female and 7 male pts. was 53 ± 19 years. Follow-up data over 59 ±17 months were compiled between 2010 and 2023.
Results: All 20 pts. achieved a hematological response i.e. partial (PR) or complete remission (CR) (as defined in Peffault de Latour et al., 2022) at 3/6/9 months after ATG as follows: PR 90%/ 75%/ 55% and CR 0%/ 20%/ 45%. Relapse of AA occurred in 60 % (12 pts.) at 24 ± 11 months after ATG, while 40 % (8 pts.) remained relapse-free during a follow up period of 59 ±17 months. In the 8 pts. without relapse, dose reduction was initiated 14 ± 6 months after ATG at a hematological response of CR in 4 pts. and PR in 4 pts. In two pts. with PR, early decrease of CsA was required due to renal insufficiency (1 month after ATG) or CsA related adverse drug reaction (4 months after ATG), respectively. The average time of CsA maintenance was 32 ± 13 months. In pts. with relapse (60%, 12 pts.), dose reduction was started after reaching best hematological response i.e. CR (9 pts.) or PR (3 pts.) at 11 ± 7 months after ATG. Relapse i.e. recurrent thrombocytopenia occurred 12 ± 9 months after start of tapering at CsA plasma levels of 44.0 ± 29.2 ng/mL and a daily CsA dosage of 1.01 ± 0.70 mg/kg. In one case, relapse occurred one month after stopping CsA. No patient with CsA levels continuously > 100 ng/mL relapsed, whereas thrombocytopenia was observed with a latency of 2.8 ± 1.6 months after first decrease below 100 ng/mL CsA in pts. with relapse. While 58% (7 pts.) of the relapsed pts. responded to salvage-therapy with CsA+Epag (age 58 ± 16 years), 42 % (5 pts.) required a second course of ATG/CsA, or transplant (age 44 ± 22 years).
Conclusion: In s/vsAA pts. with hematological response to ATG/CsA, closer monitoring for relapse is recommended reaching CsA plasma levels <100 ng/mL, as CsA <100 ng/mL was associated with higher risk of relapse during CsA tapering in line with previous reported in vitro data. Pending prospective validation, CsA plasma levels >100 ng/mL might serve as threshold in pts. requiring accelerated tapering due to renal insufficiency or CsA related side effects.

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