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Vaccination efficacy after allogeneic haematopoietic stem cell transplantation (VaccHemInf cohort): importance of haematologic characteristics for vaccine immunogenicity

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Background: Recipients of allogeneic haematopoietic stem cell transplant (allo-HSCT) are at high risk of developing life-threatening invasive infections. An important heterogeneity in immunogenicity is expected as vaccine response may vary according to the characteristics of allo-HSCT (conditioning, type of donor, stem cell source), the transplant-related complications such as graft-*versus*-host disease (GVHD) requiring the use of immunosuppressive drugs. This study aimed to assess vaccination efficacy after allo-HSCT.

Material/methods: In this single-centre, prospective, observational study, allo-HSCT recipients were referred to a consultation dedicated to immunosuppressed host immunization. Were evaluated the vaccine immunogenicity of the 3 one month apart recommended injections of: (i) the 13-valent pneumococcal conjugate vaccine; and (ii) the penta- or the hexavalent combination vaccine including diphtheria, tetanus, pertussis, poliomyelitis, *Haemophilus influenzae* b and viral hepatitis B in seronegative recipients. For each vaccine, immunoglobulin G (IgG) concentrations were assessed from blood samples taken immediately before and 3 to 6 months after vaccination. In addition, blood T, B and NK cell counts were performed at vaccination. Wilcoxon matched-pairs signed rank test was

used to compare antibody titres before and after vaccination, and Mann-Whitney U test assessed differences between the study groups, as appropriate. A *p*-value< 0.05 was taken as significant.

Results: The 32 included patients (19 males, 59.4%; mean age, 45.9 [95%CI, 40.5-51.2] year-old) received their first vaccine injection at a mean delay of 14.9 (95%CI, 11.8-18.0) months after allo-HSCT. Main reasons for delay in recipient's inclusion in the vaccination schedule were extensive GVHD (n=12, 37.5%), infectious complications (n=10, 31.3%), intravenous immunoglobulin administration (n=9, 28.1%) and completion of immunosuppressive treatment (n=2, 6.3%). At time of vaccination, a normalization of T CD4+, T CD8+, B and NK cell counts was observed in 13 (40.6%), 27 (84.4%), 26 (92.9%) and 23 (82.1%) patients, respectively. Immunogenicity evaluation was performed 3.9 (95%CI, 3.4-4.3) months after the last vaccine injection. Among pre-transplant characteristics, conditioning regimen including anti-thymocyte globulins resulted in a non-significant rise of pneumococcal antibodies after full vaccination (*p*=0.320). Cord blood unit recipients (n=6, 18.8%) showed a poor magnitude of pneumococcus, tetanus and diphtheria vaccine response in comparison with peripheral (n=14, 43.8%) and bone marrow (n=12, 37.5%) stem cell recipients. Recipients with extensive GVHD (n=16, 50.0%) had a significantly decreased vaccination response to pneumococcus (*p*=0.017), tetanus (*p*=0.045), and diphtheria (*p*=0.010), especially when undergoing extracorporeal photopheresis.

Conclusions: Haematological characteristics and transplant-related complications greatly impact vaccine immunogenicity after allo-HSCT. In particular, extensive GVHD critically decreases immunization response to most vaccine targets, despite vaccination initiation postponing. These findings argue for specific vaccination schedules in case of extensive GVHD after allo-HSCT.