Etanercept treatment and monocytopenia increase the risk for invasive aspergillosis in patients after allogeneic stem cell transplantation

Tamara Zoran1,2, Michael Weber2,3, Jan Springer1, P. Lewis White4, Joachim Bauer1, Annika Schober1, Claudia Löffler1, Bastian Seelbinder3, Kerstin Hünninger5,6, Oliver Kurzai5,6, André Scherag7, Sascha Schäuble3, C. Oliver Morton8, Hermann Einsele1, Jörg Lind6,8, Jürgen Löffler1#

1University Hospital Würzburg, Medical Hospital II, WÜ4i, Würzburg, Germany 2Friedrich Löffler Institute, Institute of Molecular Pathogenesis, Jena, Germany 3Leibniz Institute for Natural Product Research and Infection Biology–Hans Knöll Institute, Jena, Germany 4Public Health Wales, Microbiology, Cardiff, UK 5Septomics Research Centre, Friedrich Schiller University and Leibniz Institute for Natural Product Research and Infection Biology–Hans Knöll Institute, Jena, Germany 6Institute for Hygiene and Microbiology, University of Würzburg, Würzburg, Germany 7Institute of Medical Statistics, Computer and Data Sciences, Jena University Hospital, Jena, Germany 8Friedrich Löffler Institute, Institute of Bacterial Infections and Zoonoses, Jena, Germany 9Western Sydney University, School of Science and Health, Campbelltown NSW 2560, Australia.

# Both authors contributed equally

Introduction
Diagnosis of invasive aspergillosis (IA), a life-threatening mold disease, remains challenging, due to poor conventional diagnosis and often non-specific clinical symptoms. The aim of our study was to identify additional risk factors that might, in combination with established diagnostic tests improve the diagnosis and management of IA in patients after allogeneic stem cell transplantation (alloSCT).

Study design

Identified risk factors for developing IA after alloSCT

Impact on immune response?

in vitro
Human monocyte-derived macrophages (MDM)
-/+ A. fumigatus
-/+ etanercept
1. Gene expression profiles
2. Cytokine responses
ex vivo
CXCL10 quantification in patient sera

Results

1 Low monocyte counts up to four weeks prior to the diagnosis of IA are significantly associated with disease.

Control data (white boxplots) was matched to the time point of alloSCT of all cases (blue boxplots) per week. Differences were determined by the Likelihood-Ratio test. Nominal significant differences (i.e. p≤0.05) were observed for all 4 weeks.

2 Presence of etanercept down-regulates genes involved in immune responses and TNF-alpha signalling in MDM infected with A. fumigatus.

Regulation of NF-κB target genes which are differentially expressed in MDM treated with A. fumigatus and etanercept (AF+ET, AF) compared to A. fumigatus (AF_MDM) only. Down-regulated genes are marked with blue color.

(a) The heatmap displays downregulation of genes after addition of etanercept and the regulatory network
(b) Summarizes the effect of etanercept on the TNF-alpha signaling pathway

3 Presence of etanercept significantly decreases the secretion of the chemokine CXCL10 from MDM infected with A. fumigatus.

Secretion of TNF-alpha (p = 0.0104) and CXCL10 (p = 0.0004) is significantly downregulated in MDM stimulated with A. fumigatus under etanercept treatment (AF, ET) compared MDM stimulated with A. fumigatus only (AF). Differences were determined by the Wilcoxon-Mann-Whitney test (p≤0.05 are highlighted by *).

Conclusions
Our study offers new insights regarding the individual risk for IA in alloSCT patients. Further validation of low monocyte counts and administration of etanercept in IA patients is necessary before such information is used for decision making regarding monitoring of patients at risk for IA or the use of antifungal prophylaxis.

Key message
• Low monocyte concentration, administration of etanercept and severe GvHD of the gut are associated with higher risk for developing IA in alloSCT patients.
• Etanercept inhibits immune responses through modulation of NFκB activity, TNF-alpha activity and CXCL10 release.

Reference