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

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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).

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 NFkB activity, TNF-alpha activity and CXCL10 release.

Study design

Identified risk factors for developing IA after alloSCT

Collection of clinical variables

Patient cohort
- alloSCT patients
- 36 probable IA cases
- 36 controls (no fungal infections)

Validation cohort
- alloSCT patients
- 23 probable IA cases
- 25 controls (no fungal infections)

Statistical analysis & model building

Monocyte count

Etanercept treatment

Severe GvHD of the gut

Impact on immune response?

in vitro

Human monocyte-derived macrophages **(MDM)**
+/- *A. fumigatus*
+/- etanercept

1. Gene expression profiles

2. Cytokine responses

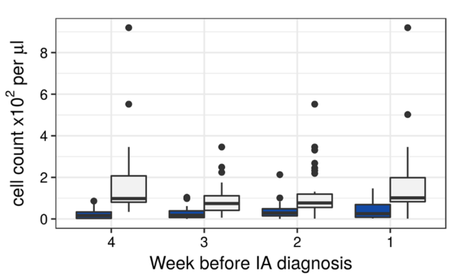
ex vivo

CXCL10

quantification in patient sera

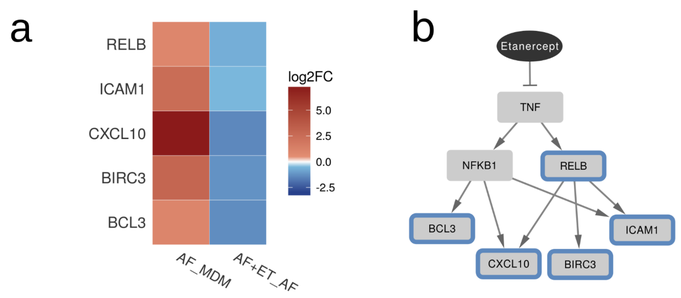
Results

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



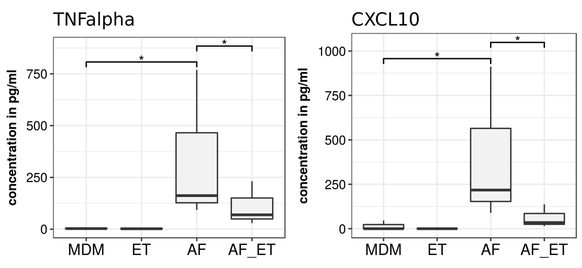
Control data (white boxplots) was matched to the time point of alloSCT of all cases (blue boxplots) per week.
Differences were determined by the Likelihood-Ratio test. Nominally significant differences (i.e. p≤ 0.05) were observed for all 4 weeks.

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



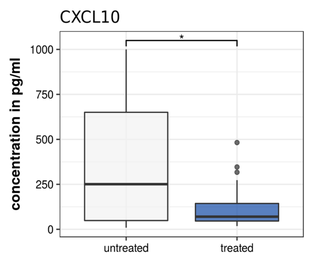
Regulation of NF-κB target genes which are differentially expressed in MDM treated with *A. fumigatus* and etanercept (AF+ET_AF) compared to *A. fumigatus* (AF_MDM) only. Down-regulated genes are marked with blue color.
(a) The heatmap displays downregulation of genes after addition of etanercept and 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 *).

IA patients under etanercept treatment have lower CXCL10 serum concentrations compared to IA patients without etanercept treatment.



CXCL10 release in serum samples from eight IA patients without etanercept treatment (untreated) and IA patients under etanercept treatment (treated).
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.

Reference

Zoran, T. *et al.* Treatment with etanercept and low monocyte concentration contribute to the risk of invasive aspergillosis in patients post allogeneic stem cell transplantation. *Sci Rep* **9**, 17231 (2019). doi.org/10.1038/s41598-019-53504-8

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WÜ4i innate immunity infection inflammation

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