

P0606 The increased risk of microbial infections in multiple sclerosis patients: interplay between disease-modifying therapies and human phagocytes

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Background: The risk infection in multiple sclerosis (MS) associated with MS treatments has become one of the most important factors in the therapy choice. The hospitalization high rates and infection-related mortality could be mainly attributed to disease-modifying therapy (DMT). DMT alters, at various extend, the innate immunity against pathogens. In this project, granted by an ESCMID research grant, the straightforward effect of the most common MS DMTs on healthy subject (HS) neutrophil functions was examined *in vitro*.

Materials/methods: To achieve this purpose HS polymorphonuclear cells (PMNs) were pre-treated with either immunosuppressive (i.e. natalizumab - NAT, fingolimod - FTY) or immunomodulatory (i.e. interferon β 1b – INF β -b, glatiramer acetate - GA) drugs, and then their functional activity was investigated. In detail, PMN intracellular killing activity towards *Klebsiella pneumoniae*, the cytokine release profile, the apoptosis, the ROS production and surface molecule expression were evaluated.

Results: *In vitro* assays with drug pre-treated HS PMNs showed a reduction in bacterial killing with statistically significantly lower values ($p < 0.001$) than those registered for the un-pre-treated controls for all the DMTs assayed (Figure 1). In the same experimental conditions variable results, depending on the DMT used, for the other examined neutrophil functions were achieved. The reduction in the intracellular killing activity of NAT pre-treated PMNs was not accompanied by changes in the other functional parameters. On the contrary, this defective neutrophil killing was also associated with a significantly lower ROS production, a slight increase of survival and cytokine production with FTY pre-treatment, and with a lower cytokine release pattern in case of both INF β -b and GA pre-treatment.

Conclusions: As microbial killing is a PMN critical physiological function, involving various mechanisms and although apoptosis, ROS, and cytokine do not seem to have an impact on the differences observed in the defective killing capacity of PMNs from treated-MS patients, other mechanisms, due to PMN plasticity, might be involved. However, our promising results regarding pre-treatment assays, confirmed that the PMN impairment is strongly linked to the treatment itself and may contribute to increase exacerbations and microbial infection onset. The balance of the overall risk *versus* benefit should be continuously re-evaluated during treatment.

Figure 1. Effect of DMTs on HS PMN intracellular killing activity (%) against *K. pneumoniae*

