2 EFFECT OF IMMUNOSUPPRESSIVE TREATMENT ON GENE EXPRESSION IN MUSCLE FROM PATIENTS WITH POLYMYOSITIS AND DERMATOMYOSITIS

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Background Polymyositis (PM) and dermatomyositis (DM) muscle tissue is characterised by infiltrating T cells, macrophages and dendritic cells, as well as cytokines, chemokines and lipid mediators forming an inflammatory milieu. Patients are treated with glucocorticoids in combination with additional immunosuppressive drugs nevertheless patients rarely reach full recovery and persistent T cells as well as IL-1 and mPGES-1 expression has been seen in muscle tissue. Here, the authors aimed to investigate whether the expression of genes related to inflammation and muscle remodeling is affected by immunosuppressive treatment in patients with PM and DM.

Patients/methods Muscle biopsies from six patients (two PM and four DM, two men and four women) taken before and after a median of 10 months (range 7, 5–16) of treatment were analysed with microarray. For verification, immunohistochemistry (IHC) and single section western blot was performed. For single section western blot, approximately 20 sections of 7 µm muscle tissue were lysed and analysed for protein content.

Results Several pathways of interest were identified by microarray:

- ▶ AIM2 inflammasome pathway is still active which could explain the persistent IL-1 expression. Upregulated genes; AIM2: 2.5 fold, Caspase 1: 2.3 fold and IL-18: 2.2 fold.
- ▶ Interferon pathway seems unaffected by immunosuppressive treatment. Upregulated genes; STAT1: 4.3 fold, CXCL10/11: 5.6/5.9 fold and IRF8: 2.8 fold.
- ▶ Changes in PGE2 signaling pathway. Upregulated gene; EP4: 2.0 fold, downregulated gene; EP3: -3.0.
- ▶ Damage of muscle fiber structural proteins. Downregulated genes; FKBP5: -3.0 fold, FOXO1A: -2.5 fold. Also several proteins involved in ubiquitination/proteasome pathway were upregulated.

The gene expression has so far been confirmed on protein level for STAT1, IRF8 and FOXO1A by IHC and for EP3 as well as EP4 protein expression by IHC and western blot.

Conclusions Persistent inflammation in muscle tissue of patients with PM or DM might be explained by insufficient effect of conventional immunosuppressive treatment on different inflammatory pathways, such as AIM2 inflammasome, interferons and PGE2. During treatment, structural muscle proteins are negatively affected and this, concurrently with the continuing inflammation might contribute to the prolonged muscle impairment in PM and DM patients.