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IDENTIFICATION OF HUB GENES AND PATHWAYS IN DERMATOMYOSITIS BY BIOINFORMATICS ANALYSIS

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Background: Dermatomyositis (DM) is a chronic systemic autoimmune disease characterized by inflammatory infiltrates in the skin and muscle¹. The genes and pathways in the inflamed myopathies in patients with DM are poorly understood². **Objectives:** To identify the key genes and pathways associated with DM and further discover its pathogenesis.

Methods: Muscle tissue gene expression profile (GSE143323) were acquired from the GEO database, which included 39 DM samples and 20 normal samples. The differentially expressed genes (DEGs) in DM muscle tissue were screened by adopting the R software. Gene ontology (GO) and Kyoto Encyclopedia of Genome (KEGG) pathway enrichment analysis was performed by Metascape online analysis tool. A protein-protein interaction (PPI) network was then constructed by STRING software using the genes in significantly different pathways. Network of DEGs was analyzed by Cytoscape software. And degree of nodes was used to screen key genes.

Results: Totally, 126 DEGs were obtained, which contained 122 up-regulated and 4 down-regulated. GO analysis revealed that most of the DEGs were significantly enriched in type I interferon signaling pathway, response to interferon-gamma, collagen-containing extracellular matrix, response to interferon-alpha and bacterium, positive regulation of cell death, leukocyte chemotaxis. KEGG pathway analysis showed that upregulated DEGs enhanced pathways associated with the hepatitis C, complement and coagulation cascades, p53 signaling pathway, RIG-I-like receptor signaling, Osteoclast differentiation, and AGE-RAGE signaling pathway. Ten hub genes were identified in DM, they were ISG15, IRF7, STAT1, MX1, OASL, OAS2, OAS1, OAS3, GBP1, and IRF9 according to the Cytoscape software and cytoHubba plugin.

Conclusion: The findings from this bioinformatics network analysis study identified the key hub genes that might provide new molecular markers for its diagnosis and treatment.

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(A) In the volcano, each dot represents a gene, blue indicates low expression genes, red indicates high expression genes, and black indicates no markedly expressed genes. (B) In the heat map, each square represents a gene, and the color indicates that the higher the expression level of the gene, the darker the color (red up, blue down). (C) The results of GO analysis show that the functions of differently expressed genes are mainly concentrated in the above 20 aspects. (D) The results of KEGG show that the functions of differently expressed genes are mainly concentrated in 12 aspects. (E, F) Among the 126 DEGs, the 10 up-regulated genes with the largest differences are ISG15, IRF7, STAT1, MX1, OASL, OAS2, OAS1, OAS3, GBP1, IRF9.

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HIGH DOSE INTRAVENOUS PULSE METHOTREXATE IN REFRACTORY EOSINOPHILIC FASCIITIS: WHAT ARE THE ADVERSE EVENTS?

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Background: Eosinophilic Fasciitis (EF) is a disease of unknown origin initially characterized by limb or trunk edema, and collagenous thickening of the subcutaneous fascia in later stages. Eosinophilia in peripheral blood is commonly observed. Being a rare disease, evidence regarding treatment is mainly based on case series and anecdotal evidence. The mainstay systemic treatment is prednisone, and Methotrexate (MTX) up to doses of 25 mg/week is the leading prednisone-sparing agent. Mycophenolate can be considered in refractory cases. As an alternative we explored the use of intravenous (i.v.) pulse MTX. We already showed this to be a potentially effective and safe treatment option in a prospective single-arm study¹, but more data on adverse events (AEs) are needed.

Objectives: To present an overview of AEs of high dose i.v. pulse MTX in refractory EF.

Methods: Adult patients with EF based on clinical appearance combined with histology and/or MRI, who were unresponsive to prednisone combined with low-dose MTX or presenting with severe disease, were selected for this retrospective cohort study. Patients received 6-9 monthly infusions of 4 mg/kg MTX followed by oral folic acid rescue therapy, which is comparable to treatment schedules for trophoblast disease. An additional number of six pulses could be administered in case of a partial effect or flare. Safety data were monitored during each visit and classified according to the Common Terminology Criteria for Adverse Events (CTCAE) from the National Institute of Health (2009).

Results: Twenty-seven patients (26 with EF, one with deep linear morphea) were included in this study (five males), with a mean age of 59 (sd 11.5) years, based on clinical presentation and histology and/or MRI. Previous treatment data were available for 22 patients of which 21 received oral prednisone (20-60 mg) whether or not combined with low dose MTX and/or UVA1 therapy. All patients reported ≥ 1 AEs at some stage, exactly 100 in total. 'Gastro-intestinal disorders' (n=36) and 'General disorders and administration site conditions' (n=15) were most common; especially nausea (n=6) and fatigue (n=11). One patient was hospitalized for blood transfusion. In four cases, treatment was discontinued due to AEs (acute kidney injury (AKI), depression, nausea/vomiting, and leukopenia resp.). Each reported AE appeared reversible. The patient with AKI had an MTX level in the toxic range; methotrexate-induced crystal nephropathy seemed the most likely explanation, probably due to a combination of high body weight (and thus high absolute dosage of MTX) and the concomitant use of omeprazole. Oral folic acid rescue therapy was prolonged, together with 500 cc i.v. fluid, after which kidney function normalized.

Organ system	AE	Frequency
Gastro-intestinal disorders	Nausea, oral mucositis, diarrhea, vomiting, abdominal pain, anorexia	36
General disorders, administration site conditions	Malaise, fatigue	15
Respiratory, thoracic, mediastinal disorders	Cough and dyspnea	10
Skin and subcutaneous tissue disorders	Skin hyperpigmentation, hair loss, alopecia, other	9
Nervous system	Headache, nerve abducens disorder	7
Infections and infestations	Skin, urinary tract, upper respiratory tract, other	6
Blood, lymphatic system disorders	Anemia, leukopenia, pancytopenia	4
Psychiatric conditions	Depression	3
Renal, urinary disorders	Acute Kidney Injury	1
Other systems		9
		100

Conclusion: AEs were common among patients receiving high dose i.v. pulse MTX, especially nausea and fatigue, but were generally mild and reversible in all cases. This is in line with studies performed with patients with trophoblast disease. One episode of reversible AKI occurred that seemed to be related to high body weight and the use of concomitant medication. The safety profile of i.v. pulse MTX thus seems auspicious, but the case of AKI illustrates that further data on safety is needed.