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Increased percentage of HLA-DR T cells in untreated juvenile dermatomyositis

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Abstract

This study investigates HLA-DR expression on activated T cells and serum neopterin levels in Juvenile Dermatomyositis (JDM) children pre- and post-treatment. Sixty-nine JDM children (less than 18 years) were included. Elevated HLA-DR+ *T* cells (>7 %) were observed in 19 % of untreated cases. Post-treatment, mean HLA-DR+ *T* cells decreased from 5.1 to 2.9 ($P < 0.001$), and serum neopterin levels declined from 19.3 to 9.1 nmol/L ($P < 0.0001$). A positive correlation between serum neopterin and HLA-DR T cell percentage was observed ($r = 0.39$, $P = 0.01$).

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Ethical approval and consent to participate

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Consent for publication

The final manuscript has been reviewed and approved by all the authors.

CRediT authorship contribution statement

Amer Khojah: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Conceptualization. **Madeline Schutt:** Writing – review & editing, Writing – original draft, Formal analysis. **Gabrielle Morgan:** Writing – review & editing, Writing – original draft, Data curation. **Ameera Bukhari:** Writing – review & editing, Writing – original draft, Formal analysis. **Nicolas Bensen:** Writing – review & editing, Writing – original draft, Formal analysis. **Aaruni Khanolkar:** Writing – review & editing, Writing – original draft, Data curation. **Lauren M. Pachman:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clicom.2024.02.002.

Intravenous steroid treatment exhibited a 47.4 % improvement in HLA-DR+ *T* cells and a 50.5 % reduction in serum neopterin levels, in contrast to 14.8 % and 34.1 % in the oral steroid group. In conclusion, treatment, particularly with IV steroids, significantly improved HLA-DR+ *T* cells percentage and neopterin levels. A correlation between HLA-DR+ *T* cells percentage and serum neopterin was noted in untreated JDM patients.

Keywords

Juvenile dermatomyositis; HLA-DR+T cell; Neopterin

Introduction

Juvenile Dermatomyositis (JDM) is a systemic autoimmune vasculopathy characterized by progressive, symmetric proximal muscle weakness and distinctive skin rash [1]. Despite extensive research, the exact underlying cause of the disease remains elusive. However, a prevailing hypothesis suggests that it arises from an inflammatory response in genetically predisposed children triggered by environmental factors such as ultraviolet light exposure or infectious agents [2–4]. Diagnosis of JDM can be confirmed with a muscle biopsy, which reveals perifascicular atrophy and diffuse infiltration by inflammatory cells [2,5]. The disease is treated mainly with corticosteroid therapy with the goal of suppressing inflammation; however, many patients develop steroid side effects over time [6]. While clinical indices such as the Disease Activity Score (DAS) [7] and the Childhood Myositis Assessment Scale (CMAS) [8] are available, there is an urgent need for accessible laboratory-based disease activity biomarkers. These biomarkers are crucial for guiding therapy decisions and identifying specific patient subsets that could potentially benefit from a more targeted therapeutic approach.

Previous studies have shown that activated T-cells (defined by co-expression of CD3 and HLA-DR) are elevated in patients with autoimmunity syndromes such as systemic lupus erythematosus (SLE) [9,10], but there are limited data on this T-cell population in JDM patients. HLA-DR is a molecule transcribed from the major histocompatibility complex type 2 (MHC-II) gene and expressed on the surface of antigen-presenting cells such as B cells, macrophages, and dendritic cells. It plays a vital role in activating adaptive immune response by presenting antigens to CD4 T-cells to instigate their clonal proliferation and subsequent differentiation [11]. Although typically expressed on antigen-presenting cells, HLA-DR is also found on activated effector T-cells in autoimmune diseases like SLE and chronic infections such as HIV and TB [9,12,13]. Furthermore, HLA-DR+ *T* cells percentage is correlated with disease activity in patients with SLE [9].

Neopterin, a pteridine compound released by macrophages, monocytes, and dendritic cells in response to interferon-gamma released by activated T-cells, represents another potential biochemical marker for T-cell activation [14,15]. Serum neopterin level is elevated in 80% of treatment naïve JDM patients and its level correlates with the disease activity scores [15]. We hypothesized that treatment naïve JDM subjects have elevated HLA-DR+ *T* cells because the majority of them have elevated serum neopterin levels secreted from

macrophages after interacting with activated T cells. The goal of this study is to assess the percentage of HLA-DR positive T-cells in a population of patients with JDM before and after medical treatment. Additionally, we aim to evaluate the correlation between the percentage of HLA-DR positive T-cells and serum neopterin level over the same time points.

Methods

This is a retrospective chart review study (IRB# 2012–14,858) at The CureJM Center and Ann & Robert H. Lurie Children's Hospital. We included all children (less than 18 years old) with JDM who met Bohan and Peter's criteria for JDM diagnosis [16] and had T and B cell flow cytometry before initiating medical therapy. Patients with overlap syndromes were excluded from the analysis. To ensure data quality, each blood sample underwent two separate flow cytometric experiments. Samples failing to exhibit matching percentages of T cells, B cells, and NK cells between the two runs were rejected due to poor quality. The first run involved the assessment of CD45, CD3, CD4, CD8, CD19, and CD16/CD56 markers. The second run, which is the focus of this study, included CD45, CD3, and HLA-DR. All antibodies for the flow cytometry tests were manufactured by BD Biosciences, San Jose, CA. Further details about the antibodies, including clone numbers and labels, are available in the supplement (see Supplementary Table 1).

Elevated HLA-DR+ *T* cells were defined by levels higher than 7 % of total T cells based on the reference range provided by the clinical immunology laboratory. We assessed HLA-DR+ *T* cells percentage at baseline (untreated) and 2–3 months after treatment. The gating strategy for quantifying HLA-DR+ *T* cell percentage is depicted in Fig. 1. Additionally, we assessed the Mean Fluorescence Intensity (MFI) of HLA-DR expression for the latest five enrolled patients (supplemental Fig1). The flow cytometry analysis software employed for these measurements was FlowJo v10. We also evaluated disease activity markers on presentation, such as DAS [7], number of nailfold capillary end row loops (ERL) [17,18] and serum neopterin level (measured competitive enzyme immunoassay) [15]. Statistical analyses were carried out using paired T-tests to compare mean T cell populations across the different time points. Pearson's correlation was used to examine the relationship between HLA-DR+ *T* cells percentage and disease activity markers. IBM SPSS Statistics 26® software and GraphPad Prism 9 software were employed for conducting the statistical analyses and generating the figures.

Results

This study was based on the analysis of 69 children (less than 18 years old) with untreated JDM, with 80 % of them being female (Table 1). The mean age at presentation was 6.7 ± 3.5 years, and the average duration of untreated disease was 8.0 ± 9.7 months (Table 2). The ethnic and racial distribution included 77 % Caucasian, 15 % Hispanic, 4 % Asian, and 1.4 % African American children. The mean age of JDM onset was 6.8 ± 3.5 years. Myositis-specific antibodies (MSAs) were identified as follows: anti-P155/140+ in 51 %, anti-MJ+ in 7 %, anti-Mi-2+ in 4 %, anti-MDA-5+ in 4 %, multiple MSAs in 9 %, and MSA negative in 23 % of the cases (Table 1). Baseline disease activity assessment of the JDM cohort is presented in table 2.

Before initiating immunosuppressive treatment, 19 % of the children with JDM exhibited elevated levels of HLA-DR+ *T* cells percentage (> 7 % of the total T cell population). However, 2–3 months post-initiation of immunosuppressive therapy, only 4 % of the children sustained elevated levels of HLA-DR+ *T* cells percentage. The mean percentage of HLA-DR+ *T* cells percentage in untreated JDM cases was 5.1 ± 2.5, which significantly decreased to 2.9 ± 1.9 after treatment ($P < 0.001$) (Fig. 2). Similar reduction was noted in disease activity markers such as DAS-total, DAS-muscle weakness, DAS-skin, ERL count and neopterin (Fig. 2a–d,f). Subsequently, Mean Fluorescence Intensity (MFI) of HLA-DR expression was calculated for the last 5 enrolled JDM patients. The MFI of HLA-DR+ *T* cells showed a significant reduction from 1599 ± 621 in untreated JDM cases to 758 ± 593 after treatment ($P < 0.033$) (Fig. 3, Supplemental Fig. 1). While no substantial correlation was identified between HLA-DR+ *T* cell levels and DAS, a weak positive correlation emerged between the serum neopterin level and the proportion of HLA-DR+ *T* cells percentage (Pearson correlation coefficient = 0.39, $P = 0.01$) (Fig. 4a). Additionally, subjects with elevated HLA-DR +ve T cells exhibited a statistically significant elevation in the mean serum neopterin level (26.6 nmol/L) in comparison to patients with normal HLA-DR+ *T* cells, whose mean serum neopterin level was 17.23 nmol/L and $P = 0.004$ (Fig. 4b).

Next, the study participants were categorized into two groups based on their corticosteroid treatment protocols: oral steroid ($n = 7$) and high-dose intravenous (IV) steroid ($n = 62$). The oral steroid group exhibited no significant change in the T cell HLA-DR expression ($P = 0.47$) or serum neopterin level ($P = 0.08$) following oral steroid treatment. In contrast, the IV steroid group exhibited a significant reduction of both T cell HLA-DR expression (5.1% vs 2.7 %, $P < 0.0001$) and serum neopterin level (20.2 ± 9.3 nmol/L vs 10.0 ± 6.2 nmol/L, $P < 0.0001$) 2–3 months after IV steroid therapy (Fig. 5a,b).

Discussion

Patients with SLE have an increased percentage of HLA-DR+ *T* cells which is linked to their disease activity [9,19]. However, the potential existence of a similar correlation in other autoimmune disorders, such as JDM, remains unexplored. In this study, we investigated the association of this activated T-cell population with disease severity in JDM both prior to and following immunosuppressive treatment. Our data suggests that the percentage of HLA-DR+ *T* cells in JDM patients significantly diminishes following the initiation of immunosuppressive therapy, especially in the high dose IV steroid group (Fig. 5). IV steroids provide an advantage over oral steroids in JDM patients with decreased nailfold capillary count because of the documented decreased GI absorption of oral steroid in patients with vasculopathy [20,21]. Decreased nailfold capillary count is a hallmark of JDM and is more prominent in patients with p155/140 (Anti-TIF1- γ) autoantibody, which is the most common autoantibody in the United States population of JDM patients [22]. The consequence of IV steroid over the oral route is its ability to induce remission faster [23], as demonstrated by the data in this study documenting that the IV steroid group had a more reduction in their activated T cell percentage than the oral steroid group.

All subjects with increased HLA-DR+ *T* cell percentage in our study also had elevated neopterin. Furthermore, there was a positive correlation between serum neopterin level and the percentage of HLA-DR+ *T*-cells percentage. This finding supports the study hypothesis that activated T cells led to macrophage activation and neopterin production. Macrophage activation is an important element of JDM pathophysiology. A prior study showed that 80 % of untreated JDM has elevated neopterin [15]. The group with elevated neopterin has more active disease, evidenced by higher DAS and muscle enzymes [15]. Furthermore, higher neopterin level has been linked to poor outcomes in anti-MDA5 dermatomyositis patients with interstitial lung disease [24].

This study highlights the critical role of T cells in JDM, shedding light on the intricate nature of its pathophysiology [25]. JDM complexity arises from the interplay of various disease facets, including endothelial cell injury [26], mitochondrial dysfunction [27,28], endoplasmic reticulum stress [29], as well as the activation of numerous immune pathways. For example, MSAs are detectable in more than half of JDM patients, and each MSA is associated with distinct clinical phenotypes [2]. Furthermore, approximately two-thirds of treatment-naïve patients show an increased B cell percentage [30], with a subset of these B cells being positive for otoferlin [31]. These otoferlin-positive B cells are particularly abundant in treatment-naïve JDM patients and can infiltrate muscle tissue [31]. The expansion of B cells is likely driven by elevated levels of serum BAFF (B-cell activating factor) [30,32], which is secreted from myeloid cells. Another important cytokine in JDM pathogenesis is type 1 interferon [33], presumably produced by plasmacytoid dendritic cells and macrophages [34,35]. Identifying the precise immunological pathways activated in JDM can have clinical significance. For example, rituximab, a B cell-depleting agent, appears to be more effective in JDM patients who test positive for MSAs [36,37]. This highlights the potential for targeted treatment strategies based on underlying immune mechanisms.

This study's limitations include the inability to assess HLA-DR expression on different T cell subsets (such as CD4 vs. CD8, memory vs. naïve) due to the existing setup of the flow cytometry experiment. Also, the study sample size is relatively small, limiting the ability to assess the correlation between HLA-DR+ *T* cells and various myositis-specific antibodies. Further research is needed to characterize these activated T cells' pathophysiological role in cytokine production and amplification of the immune response.

In conclusion, HLA-DR+ *T* cell percentage and serum neopterin in JDM improves after initiating the medical treatment, especially in the IV steroid group. The percentage of HLA-DR+ *T* cells was directly associated with the concurrent serum neopterin levels.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Dr. Amer Khojah, analyzed the de-identified data while he was on the staff of Ann & Robert H. Lurie Children's Hospital of Chicago, with manuscript completion while at Umm Al-Qura University, College of Medicine, Mekkah, Saudi Arabia.

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Data availability

Data will be made available on request.

Abbreviations:

HLA-DR	Human Leukocyte Antigen – DR isotype
JDM	Juvenile Dermatomyositis
SLE	Systemic Lupus Erythematosus
HIV	human immune-deficiency virus
DAS	Disease Activity Score
CMAS	Childhood Myositis Assessment Scale
ERL	nailfold capillary end row loops
MHC-II	major histocompatibility complex type 2
MSAs	Myositis specific antibodies
IBM SPSS	International Business Machines Corporation Statistical Package for the Social Sciences

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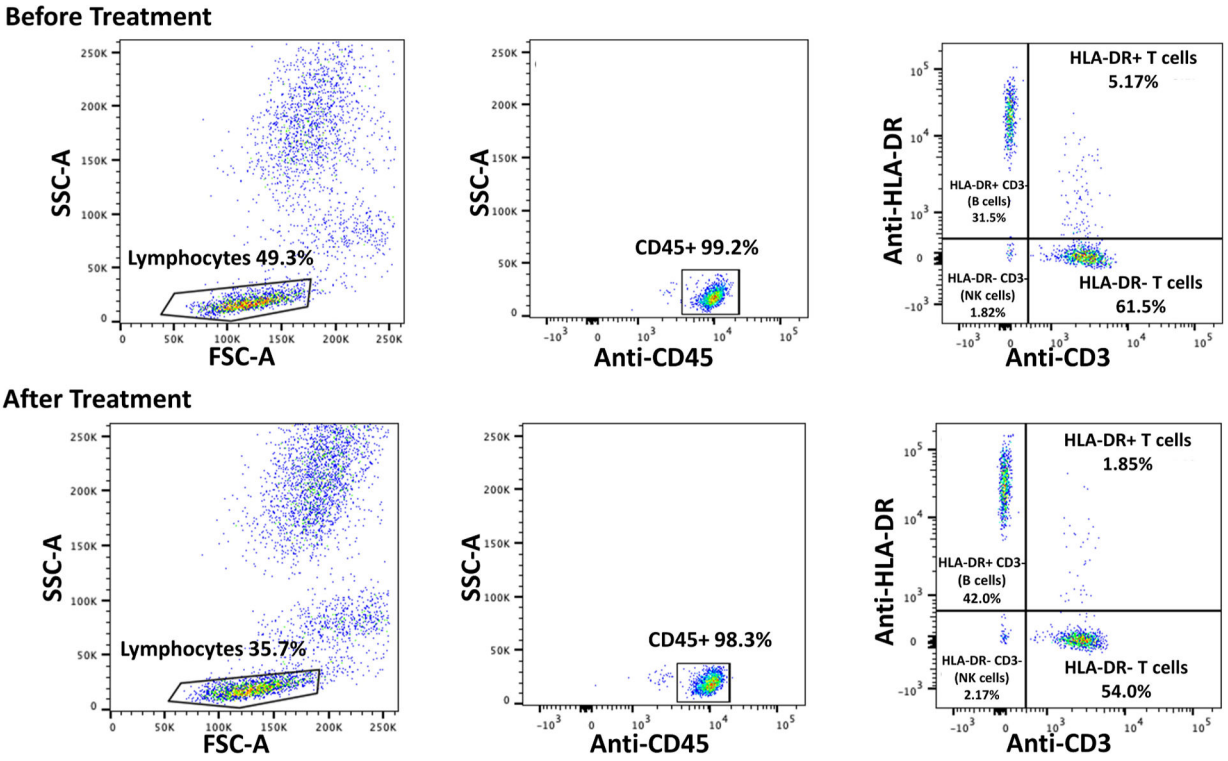

Fig. 1.

The gating strategy for HLA-DR-positive T cells. An example of the gating strategy from one of the JDM patients which demonstrates a notable decrease in the percentage of HLA-DR-positive T cells, dropping from 5.2 % before treatment to 1.9 % after treatment.

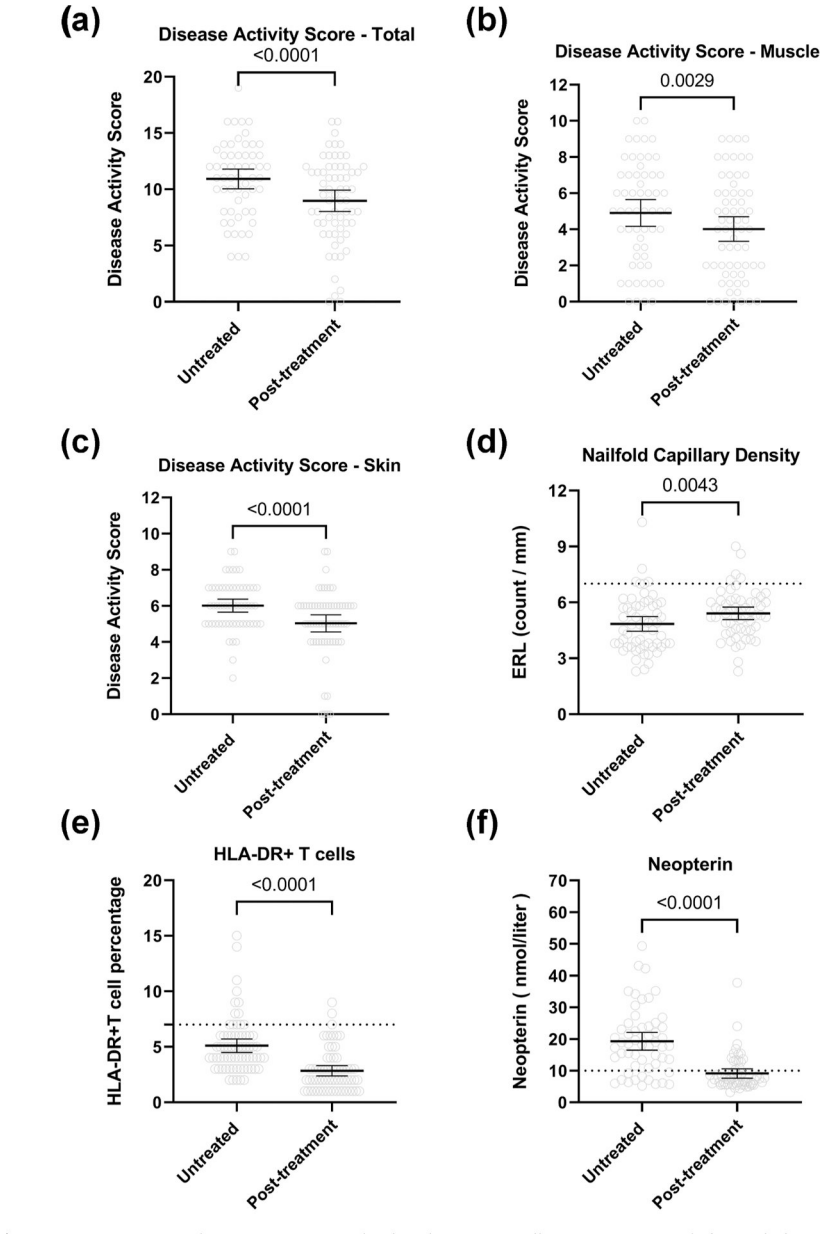

Fig. 2.

Disease activity markers, serum neopterin level, and HLA-DR T cell percentage in JDM before and after treatment.

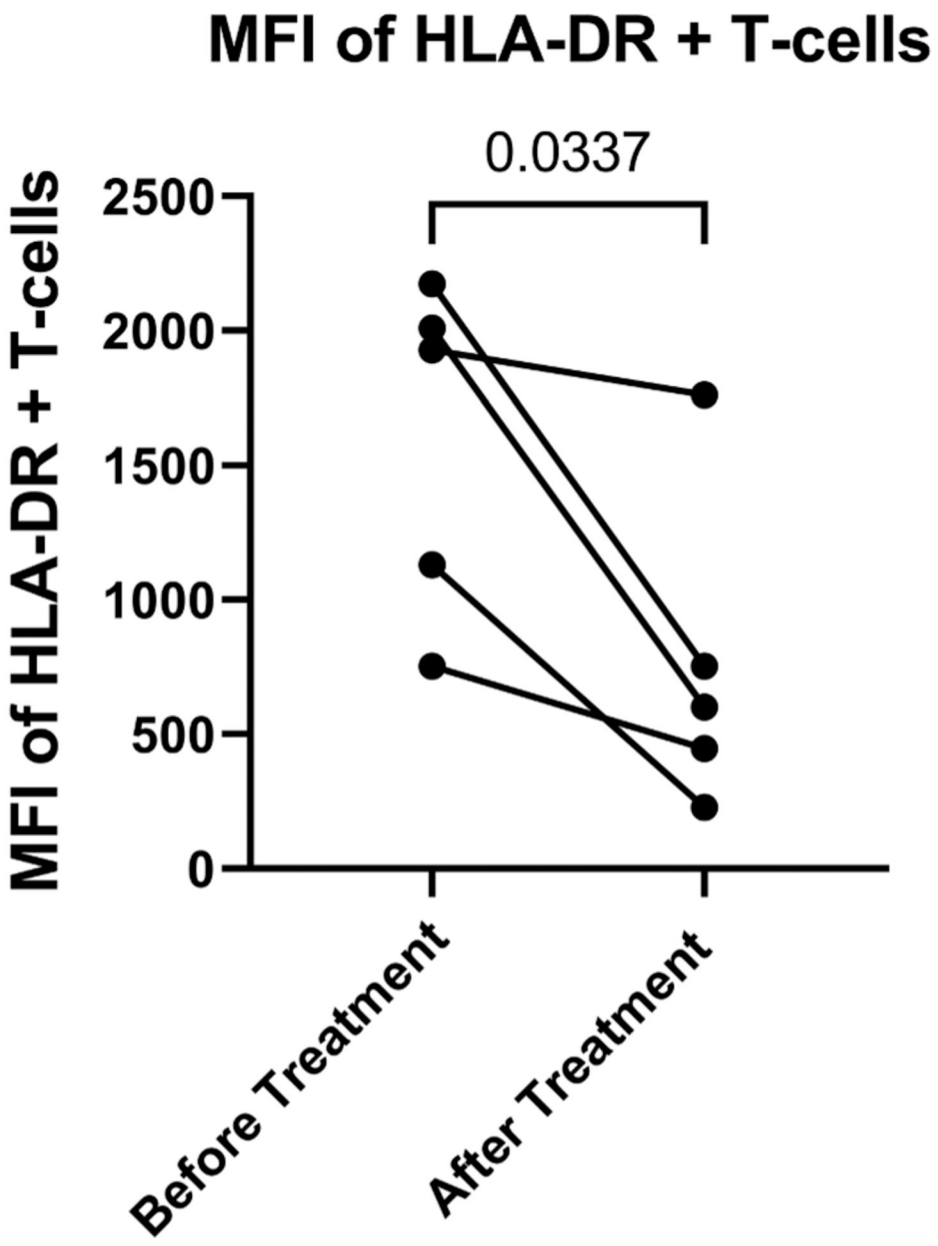

Fig. 3.

Mean Fluorescence Intensity (MFI) of HLA-DR expression by flow cytometry on 5 JDM children. The MFI of HLA-DR+ *T* cells showed a significant reduction from 1599 ± 621 in untreated JDM cases to 758 ± 593 after treatment ($P < 0.033$).

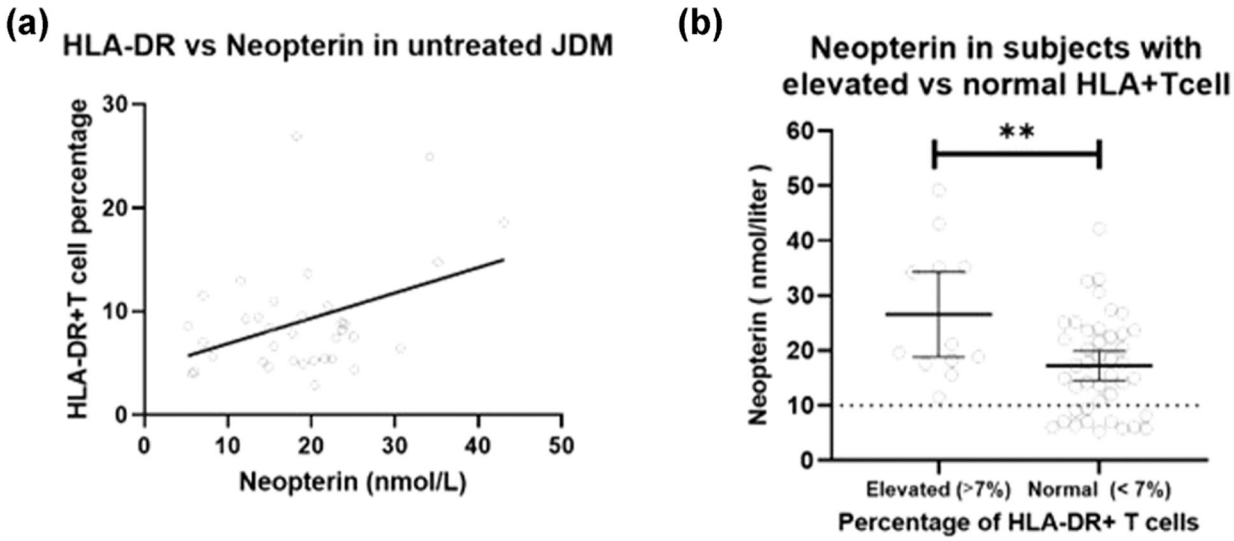

Fig. 4.

The relationship between serum neopterin and HLA-DR+ *T* cell in JDM. a) There was a positive correlation between the serum neopterin level and HLA-DR T cell percentage (Pearson correlation coefficient = 0.39, $P = 0.01$). b) Subjects with elevated HLA-DR +ve T cells had a statistically significant elevation in the mean serum neopterin level (26.6 nmol/L) in comparison to patients with normal HLA-DR+ *T* cells with mean neopterin of 17.23 nmol/L and $p = 0.004$. Of note, ** means $p < 0.01$.

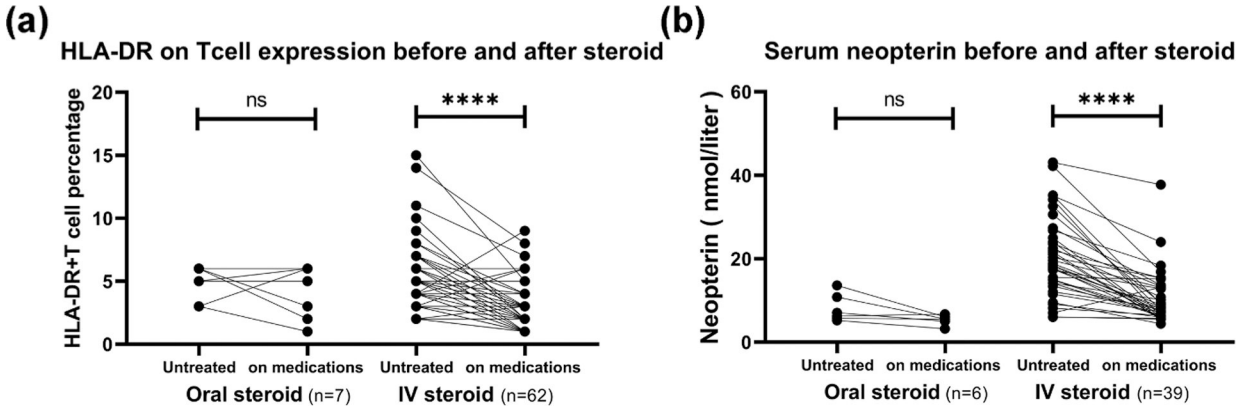

Fig. 5.

The percentage of HLA-DR +ve T cells and Serum neopterin in JDM before and after treatment. Of note, **** means $p < 0.0001$.

Table 1

Demographic and disease characteristics of the JDM cohort.

	Frequency (*n*)	Percentage
Sample size	69	
Sex		
Female	55	79.7 %
Male	14	20.3 %
Race/Ethnicity		
White	53	76.8 %
Hispanic	10	14.5 %
African American	1	1.4 %
Others	5	7.3 %
Myositis specific antibodies		
P155/140	35	50.7 %
MJ	5	7.2 %
Mi2	3	4.3 %
MDA5	3	4.3 %
Others or multiple MSAs	7	10.1 %
Negative	16	23.2 %

Table 2

Baseline (before treatment) disease activity assessment of the JDM cohort.

	Reference Range	Mean ± SD	Median (range)
Age (years)		6.9 ± 3.5	6.2 (2.3−16.9)
Duration of untreated disease (months)		8.0 ± 9.7	5.5 (0.6−73)
Clinical disease activity indicator			
DAS-total	0	11 ± 3.3	11 (4−19)
DAS-skin	0	6.0 ± 1.4	6 (2−9)
DAS-muscle	0	4.8 ± 2.8	5 (0−10)
CMAS	52	34.3 ± 12.4	37 (12−52)
ERL (#/mm)	>7	4.8 ± 1.5	4.8 (2.3−10.3)
Laboratory disease activity indicators			
Neopterin (nmol/L)	<10	19.3 ± 10.3	18.2 (5.2−49.3)
vWF Antigen		145 ± 66.6	137 (54−374)
Flow cytometry			
Total T cells (CD3+)		64.6 ± 8.9	64 (41–88)
T helper cells (CD3+ CD4+)		43.9 ± 8	43 (26−60)
T cytotoxic cells (CD3+ CD8+)		19.0 ± 5.0	19 (6−33)
CD4/CD8 Ratio		2.5 ± 1.0	2.2 (1−6.1)
Activated T cells (CD3+ HLA-DR+)		5.1 ± 2.5	5 (2−15)
B cells (CD19+)		28.7 ± 8.5	29 (8−50)
NK cells (CD16+/CD56+)		5.9 ± 3.5	5 (1−15)