HHS Public Access

Author manuscript

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2024 October 01.

Published in final edited form as:

Arthritis Care Res (Hoboken). 2023 October ; 75(10): 2082–2087. doi:10.1002/acr.25132.

HLA DRB1*15 and Eosinophilia are Common Among Patients with Systemic Juvenile Idiopathic Arthritis

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Abstract

Objective: Concern exists that medications used to treat patients with systemic juvenile idiopathic arthritis (SJIA), particularly IL-1 and IL-6 blocking agents, might be causing adverse drug reactions and lung disease (SJIA-LD). Carriage of HLA DRB1*15 has been reported as a risk factor for adverse drug reactions among patients with SJIA. We performed a retrospective chart review to evaluate these factors at our center.

Methods: We reviewed the records of 86 subjects with SJIA followed for at least 6 months between 1996 and 2022. HLA typing was performed in 23 of the subjects. We compared characteristics of patients with or without eosinophilia. Among patients with HLA typing, we compared clinical characteristics of subjects with or without DRB1*15 and with or without SJIA-LD.

Results: Among the 23 patients with HLA typing, 74% carried DRB1*15, and 63% of patients without SJIA-LD carried DRB1*15. Seven subjects had SJIA-LD, all of whom carried DRB1*15. Patients with SJIA-LD were younger at the time of diagnosis and more likely to have had macrophage activation syndrome. Exposure to IL-1 and IL-6 blockers was common, occurring in 95% of patients. Eosinophilia occurred in 39% of patients with SJIA, often before IL-1 or IL-6 blockade. Eosinophilia was associated with adverse drug reactions and macrophage activation syndrome. There was one death, unrelated to active SJIA disease.

Conclusion: Carriage of DRB1*15 was more common in this cohort of patients with SJIA than in the general population. Eosinophilia and SJIA-LD were more common among patients with severe SJIA complicated by macrophage activation syndrome.

Over the last two decades, some children with systemic juvenile idiopathic arthritis (SJIA) have developed a severe form of interstitial lung disease (ILD) termed SJIA-associated lung disease (SJIA-LD) (1–3). This has paralleled increased use of biologic agents targeting

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IL-1 and IL-6 to treat SJIA, leading to concern that these medications might predispose to SJIA-LD. In retrospective analyses, the majority of patients with SJIA-LD have had exposure to IL-1 and IL-6 inhibitors, but interpreting the relevance of this drug exposure history is confounded by the increasingly widespread use of these agents to treat SJIA over the same time period (1–3).

Recently, Saper and colleagues reported an association between carriage of the class II major histocompatibility complex allele DRB1*15 and the development of eosinophilia, SJIA-LD, and non-evanescent rashes different from the typical SJIA rash after exposure of patients with SJIA to IL-1 and/or IL-6 inhibitors (4). The authors classified these reactions as drug-reactions with eosinophilia and systemic symptoms (DRESS). Over 80% of patients with SJIA and a history of DRESS-like reactions expressed a DRB1*15 allele, whereas only 7% of drug-tolerant patients with SJIA did. These observations have led to several working hypotheses to explain the potential mechanisms by which DRB1*15 might lead to apparent drug reactions to IL-1 or IL-6 blocking agents in patients with SJIA (4, 5).

Given the degree of clinical concern raised by the prior report (4), we began performing HLA typing on patients with SJIA routinely at our center in the autumn of 2021. Of note, some patients with more severe disease including SJIA-LD had previously undergone HLA typing. We observed in routine clinical practice that many patients with SJIA carried DRB1*15:XX. We therefore designed this retrospective study with the primary objective of reporting the carriage rate of DRB1*15:XX among patients with SJIA at our center compared to the general population carriage rate. In addition, we performed a chart review of patients with confirmed SJIA seen at our center since 1996, regardless of whether HLA typing had been performed, with the objective of describing their drug-exposure history, incidence and type of adverse drug reactions, and incidence and timing of eosinophilia in relation to each other and in relation to DRB1*15:XX carriage status. Furthermore, we sought to determine the incidence of SJIA-LD in our cohort and to evaluate its association with previously reported risk factors including DRB1*15:XX carriage, young age of disease onset, and episodes of macrophage activation syndrome (MAS). Here we describe our findings because we believe they provide critical information for the field, and we acknowledge the limitations inherent in our retrospective study design.

Patients and Methods

Study Design

We conducted a retrospective cohort study. The study design was reviewed by the University of Minnesota IRB and deemed exempt from IRB oversight.

Study Population

Subjects were considered for inclusion if they received a billing diagnosis code for SJIA between 1996 and 2022 (ICD-10-CM codes: M08.20, M08.2A, M08.29) before the age of 17 and had at least six months of follow-up in the University of Minnesota pediatric rheumatology clinics. 124 patients had diagnosis codes for SJIA during the time interval of interest. Cases were manually adjudicated to confirm the diagnosis of SJIA and to confirm

a minimum of 6 months of follow-up at our center. This 6-month minimum was chosen both to ensure the diagnosis of SJIA was confirmed and to allow time to observe potential responses/reactions to medications. Among the 124 patients with SJIA, we excluded a total of 38, including 7 with new diagnoses of SJIA who have not yet been followed for 6 months, 6 with more remote diagnoses of SJIA who were not followed for at least 6 months, 9 who were determined to have an alternative diagnosis, 4 diagnosed at age 17 years of age or older, 6 never followed by our pediatric rheumatology service, and 6 with medical records too sparse to determine if the patient had confirmed SJIA. After exclusion, 86 patients met criteria for further analysis. Data were abstracted from medical records into a secure spreadsheet. Three patients with SJIA-LD in our cohort were previously reported (3, 4).

Data Extraction

The primary source of information was the rheumatologist's clinical documentation. To determine HLA DRB1 typing status, charts were searched for "HLA" and "DRB1." Searches for whole exome sequencing or geneticists' notes were also performed. The terminology DRB1*15:XX denotes DRB1*15:01 and DRB1*15:03.

For drug exposure history, we reviewed the treatment timeline in the rheumatologists' notes and the full prescribing history. We performed chart searches for "anakinra," "tocilizumab," "rilonacept", and "canakinumab." The timing of medication initiation and cessation were abstracted directly from the prescribing records in the electronic medical record whenever possible; when a medication initiation or cessation occurred outside of our system, the dates described in the primary rheumatologist's notes were used. The development of MAS and eosinophilia were examined in relationship to these prescribing patterns.

We defined eosinophilia as an absolute eosinophil count ε700/microliter or eosinophils ε10% of the total white blood cell count. We also performed a chart search for "eosinophilia" and "eosinophil". Eosinophilia was defined as related to MAS if it occurred within two weeks prior to the diagnosis of MAS or if eosinophils remained elevated during an episode of MAS then decreased with MAS treatment.

To identify possible drug reactions, we reviewed the rheumatologist's notes and the allergy section of the chart. Additionally, we searched for the terms "drug allergy", "medication allergy", "drug reaction", and "medication reaction." We defined a drug reaction as a local injection site reaction, elevated AST or ALT (grouped here as liver function tests [LFTs]) without other explanation such as SJIA disease activity or MAS, rashes atypical for SJIA (e.g. non-evanescent, pruritic, urticarial), or acute transfusion reactions (respiratory distress or swelling during or near time of medication administration). One atypical drug reaction included diarrhea, convulsions, and confusion.

To identify subjects with SJIA-LD, search terms included "lung disease," "fibrosis," and "interstitial", plus review of any prior chest CT studies.

Statistical analysis

We tested whether the carriage rate of DRB1*15XX was equal to the general population average of 25% (6) using a binomial test. To test the null hypothesis that age was the same

between two groups of patients we used a two-sample t-test. For all other variables, we tested for differences in proportions using a chi-square test when all expected counts were greater than five, and a Fisher's exact test otherwise. The reported p-values are not adjusted for multiple testing, and therefore should be considered exploratory, rather than confirming any specific hypothesis.

Results

We identified 86 patients with SJIA who met our inclusion criteria. Seven of the 86 patients (8%) had SJIA-LD. There was one death in a patient who had undergone bone marrow transplantation for SJIA; this patient did not have SJIA-LD and had stable engraftment with no residual SJIA activity prior to death.

To date, we have performed HLA typing in 23 patients, including all 7 with SJIA-LD. These patients are shown in Table 1. A large fraction of SJIA expressed DRB1*15:XX (17/23 = 74%). This included 15 with DRB1*15:01, 1 with DRB1*15:03, and 1 in whom subtyping beyond DRB1*15 was not provided. All 7 patients with SJIA-LD carried DRB1*15. Among the patients without SJIA-LD, the rate of DRB*15:XX carriage was 10/16 (63%). For both patients with and without SJIA-LD, the proportion that expressed DRB1*15:XX is larger than the general population average of 25%, with $p<0.01$ in both cases (6). Similar to other reports, patients with SJIA-LD were younger at diagnosis and more likely to have had MAS. Trisomy 21 has been identified as a potential risk factor for SJIA-LD (2, 3). In our cohort 3 patients had trisomy 21; all 3 expressed DRB1*15:01 but none has developed SJIA-LD. Among patients with HLA typing, eosinophilia was somewhat more common in patients with SJIA-LD than those without (71% vs 50%), although this did not reach statistical significance.

We next evaluated the association between exposure to IL-1 or IL-6 inhibitor therapy, eosinophilia, and drug reactions. As shown in Table 2, the vast majority of all 86 SJIA patients (95%) were treated with IL-1 or IL-6 inhibitors, including 60/86 (70%) treated with anakinra, 52/86 (60%) with tocilizumab, and 29/86 (34%) with canakinumab. Thirty-nine patients (45%) received more than one of these agents. Eosinophilia was common in our cohort (33/86, 39%); its timing in relation to drug exposure is described later. Patients with eosinophilia were more likely to have had MAS and a history of a drug reaction.

Apparent adverse reactions to IL-1 or IL-6 blocking agents occurred in 17 of 86 patients; one additional patient had an adverse reaction to the IFNγ inhibitor emapalumab. HLA typing was performed in 12 of these 18 patients with drug reactions – 9/12 patients (75%) expressed DRB1*15:XX, whereas 3/12 (25%) did not. Nine patients had adverse reactions to anakinra, including 7 systemic reactions and 2 local injection site reactions; 3 of these reactions occurred in DRB1*15:XX positive patients (1 LFT elevation, 2 atypical rash), 2 in DRB1*15:XX negative patients (1 pruritus and 1 reaction described as confusion, diarrhea, and convulsions), and 4 who did not have HLA typing (1 with atypical rash and LFT elevation, 1 with petechial rash and eosinophilia, and 2 local injection site reactions). Eight patients had adverse reactions to tocilizumab, including 5 in DRB1*15:XX positive patients (2 LFT elevation, 1 urticarial rash, 2 respiratory distress during medication infusion), 1 in

a DRB1*15:XX negative patient (atypical rash), and 2 in patients without HLA typing (1 infusion reaction, 1 LFT elevation). None of these patients met clinical criteria for DRESS. This led to discontinuation of the suspected offending drug in 12 of 18 patients. Medications used after patients had an adverse reaction to anakinra included methotrexate, tocilizumab, canakinumab, and ruxolitinib. Medications used after patients had an adverse reaction to tocilizumab included canakinumab, abatacept, and emapalumab.

We next sought to evaluate the potential association between DRB1*15:XX carriage, eosinophilia, and drug reactions. To avoid skewing our data based on the fact that all patients with SJIA-LD had undergone HLA typing, we excluded them from this analysis. Among the 16 patients without SJIA-LD who had HLA typing performed, age at diagnosis did not differ between DRB1*15:XX carriers and non-carriers (Table 3). In this group, the rates of eosinophilia were similar among DRB1*15:XX carriers (5/10 [50%]) and non-carriers (3/6 [50%]). For comparison, among patients without HLA typing, the incidence of eosinophilia was 20/63 (32%). We also observed similar rates of drug reactions in DRB1*15:XX carriers (3/10 [30%]) and non-carriers (3/6 [50%]).

We next sought to describe the timing of eosinophilia in relation to exposure to IL-1 or IL-6 inhibitor therapy. To evaluate this, patients had to have laboratory data available prior to initiation of these agents. Of the total 33 patients with eosinophilia, 4 lacked pre-treatment data and 1 was not exposed to IL-1 or IL-6 inhibitors. Among the remaining 28 patients, eosinophilia occurred prior to IL-1 or IL-6 blockade in 12 (43%). Six of those 12 patients had resolution of eosinophilia after initiation of therapy, whereas the other 6 had some degree of ongoing eosinophilia. Table 4 compares the 12 patients who had eosinophilia prior to initiation of therapy to the 16 patients who had eosinophilia only after initiation of therapy. Importantly, we identified no significant differences between these two groups. Ten of the 33 total patients with eosinophilia had a history of MAS, and eosinophilia occurred during MAS in 5/10 (50%) of them. We also examined the relationship between the development of MAS and the initiation of anti-IL-1 or anti-IL-6 therapy. In the 15 patients who had MAS during their clinical course, 5 patients had MAS before initiation of treatment but not after, 3 patients had MAS both before and after initiation of treatment, and 7 patients had MAS only after initiation of treatment.

Discussion

The most striking finding in this cohort of patients with SJIA is the high rate of DRB1*15:XX carriage (74%). Even among subjects without lung disease, the rate of DRB1*15:XX carriage was high (63%). This rate is similar to that reported by the Boston Children’s Hospital group (7). In our cohort, all 7 patients with SJIA-LD expressed DRB1*15:XX. Eosinophilia was also common, occurring in 39% of all patients with SJIA and often prior to IL-1 or IL-6 inhibitor therapy.

One limitation of our retrospective study is the relatively small sample size, particularly the number of patients who had HLA typing performed. Because of this, several comparisons have wide confidence intervals for effect size, indicating uncertainty about the true association, or potential lack thereof. A larger sample is needed to identify differences in

characteristics between DRB1*15:XX carriers and non-carriers. We also note that for those without SJIA-LD, the patients that were HLA typed were those who were evaluated after autumn 2021. This could potentially lead to biased results if the patients who have visited the clinic after this date are systematically different from those who have not, but we do not have a reason to believe this is the case.

A very high fraction (95%) of subjects in our cohort were exposed to IL-1 or IL-6 inhibitors. Apparent drug reactions of any type occurred in 21% of our cohort, with 19% having a systemic reaction and 2% having local injection site reactions only. Of note, 6 of the 7 patients with SJIA-LD had a history of a drug reaction during their clinical course – 2 had reactions to anakinra, 3 to tocilizumab, and 1 to emapalumab. Notably, the drug reactions occurred after the diagnosis of SJIA-LD in 2 of these 6 patients. One patient with SJIA-LD had no history of drug reactions. In the report by Saper and colleagues, all subjects with lung disease scored as having DRESS during treatment with IL-1 and IL-6 inhibitors. In contrast, none of our patients with SJIA-LD were diagnosed with DRESS.

A critical issue is whether many patients with SJIA are developing DRESS in the setting of IL-1 or IL-6 inhibitors or not. The cohort in which the association of DRESS and DRB1*15 was first reported was, by design, enriched for subjects with probable drug reactions to IL-1 or IL-6 blocking agents. The authors applied RegiSCAR scoring criteria for DRESS and considered subjects with scores ε4 to have “probable DRESS” (4, 8). They reported 94 total patients with SJIA or adult onset Still’s disease (AOSD) in whom HLA typing was performed. Among these, 64 (68%) were considered to have had probable DRESS, including 45 with lung disease. The other 30 (32%) were classified as drug tolerant controls. It was this classification that led to the conclusion that HLA DRB1*15:XX was enriched among subjects with “Still’s-DRESS” cases relative to “drug tolerant” controls as well as to a larger global SJIA genetic repository – the International Childhood Arthritis Genetics Consortium (INCHARGE) (4).

A challenge with applying the RegiSCAR scoring for DRESS to patients with SJIA, as we have highlighted (5), is the shared features of the two conditions, including lymph node enlargement, “organ involvement” such as elevated liver enzymes or splenomegaly, and exclusion of other potential etiologies such as infections. Adding eosinophilia and/or characteristic DRESS rash elevates the score to at least 4, leading to classification as “probable DRESS”, although the majority of subjects reported by Saper did have RegiSCAR scores of 6 or higher (4). The high rate of eosinophilia in our cohort (39%) is notable in this regard. Thus, the key issue is whether these patients truly have DRESS reactions to IL-1 or IL-6 blockers, or whether the same symptoms and signs – particularly eosinophilia – are simply common manifestations of SJIA, a notion supported by our finding that 43% of patients with eosinophilia had it prior to IL-1 or IL-6 blockade. It is also possible that eosinophilia could arise due to the biologic activity of IL-1 or IL-6 blockade, as proposed in the Cytokine Plasticity Hypothesis (5).

If one analyzes the Saper cohort through the lens that eosinophilia is common among patients with SJIA, a different conclusion can be reached. Specifically, among all 94 SJIA and AOSD subjects with HLA typing performed, 52 of them (55%) carried DRB1*15:XX

(4). That carriage frequency is on par with the data we report here (74%) and those from Boston Children's (49%) (7), although again the Saper cohort was intentionally enriched for subjects considered to have probable drug reactions. Those carriage frequencies are all higher than those reported in the INCHARGE cohort (~25%) as well as those reported in a recent abstract with 65 Dutch patients (26%), and also higher than those reported for the general US population (DRB1*15 allele frequency in the US White population is 15.8%) (4, 6, 9, 10). It is possible that these findings could be due to differences in demographic or ancestral characteristics of the populations, although this seems unlikely since all were predominantly White. Of note, the three studies reporting higher rates of DRB1*15:XX carriage, including this one, were retrospective and applied chronicity metrics for study inclusion (4, 7). Similarly, the subgroup of patients who had HLA typing performed in these studies included a higher fraction of subjects with SJIA-LD compared to the entire SJIA cohorts, so are enriched for patients with more severe disease. In contrast, the Dutch study was prospective, and thus may have been more likely to enroll subjects with shorter disease duration (so-called "monophasic" SJIA). The Dutch cohort also included only one subject with SJIA-LD (10). Considering these factors, we hypothesize that DRB1*15:XX might not represent a risk factor for adverse reactions to IL-1 or IL-6 inhibitors, but rather a risk factor for more chronic or severe SJIA. The other MHC class II allele previously identified as a risk factor for SJIA is DRB1*11 (9). Considered these data alongside ours, it seems that both DRB1*11 and DRB1*15:XX are enriched among patients with SJIA relative to the healthy control population, and that DRB1*15:XX might also increase the risk of more severe disease.

How might DRB1*15:XX promote chronic or severe SJIA? MHC class II molecules present antigens to CD4+ T cells. We envision that patients with SJIA and DRB1*15:XX may harbor populations of CD4+ T cells that recognize particular, non-drug DRB1*15:XX-presented endogenous or exogenous antigenic peptides, for instance from the microbiome or common infectious agents. As proposed in the Cytokine Plasticity Hypothesis (5), introduction of IL-1 or IL-6 blocking agents may alter the cytokine production profile of those T cells in ways that promote eosinophilia (e.g. Th2 skewing) and/or MAS and SJIA-LD (e.g. Th1 skewing with overproduction of IFNγ and IL-18). A current challenge to the field is to define these hypothetical DRB1*15-presented antigens and to identify and better characterize the responding T cell populations. It is of course plausible that DRB1*15:XX could promote more severe SJIA through other mechanisms, but to date none has been hypothesized.

If DRB1*15:XX is indeed a risk factor for more chronic or severe SJIA including SJIA-LD, how would that inform clinical practice? We suggest that HLA typing may be useful at the time of diagnosis. Based on our data and clinical experience, we feel that patients who carry DRB1*15:XX can still be treated with IL-1 or IL-6 blockers, but concomitant use of corticosteroids or traditional non-biologic DMARDS such as methotrexate should be considered. Careful monitoring for the development of SJIA-LD, particularly in younger patients and those with macrophage activation syndrome, would be reasonable.

Funding:

AML was supported by an Arthritis Foundation “Cultivating a New Generation of Rheumatologists” Fellowship Training Award. BWL and the Clinical and Translational Science Institute were supported by NIH grant UL1TR002494.

Conflicts of Interest:

BAB is a site principal investigator for a clinical trial sponsored by Sobi; SAM, PMH, and MMR are co-investigators on that study.

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Significance and Innovation

- The prevalence of HLA-DRB1*15:XX carriage in our patients with SJIA was higher than in the general population.
- Eosinophilia was relatively common in our cohort (39% percent), often occurred prior to IL-1 or IL-6 inhibitor therapy, and did not differ based on the presence or absence of HLA-DRB1*15:XX.
- Many patients who carried HLA-DRB1*15:XX did not have eosinophilia, adverse drug reactions, or lung disease despite 95% of all patients being exposed to IL-1 or IL-6 inhibitors.
- In our cohort, all patients with SJIA-LD expressed HLA-DRB1*15:XX and were also significantly younger at age of diagnosis and more likely to have had a history of MAS.

TABLE 1

Comparison of patients with SJIA with lung disease (SJIA-LD) to those without lung disease

	SJIA patients with HLA DR Typing (n=23)			
	SJIA-LD n=7	**No Lung Disease n=16**	**Mean difference (CI)**	**P-value (lung disease vs no lung disease)**
Age at Diagnosis (y) (mean, range)	1.7, (1–3)	7.4, (1–16)	−5.7 (−9.7,−1.7)	0.01
			Odds ratio (CI)	
HLA DRB1*15:XX positive (N, %)	7 (100%)	10 (63%)	Inf (0.6, Inf)	0.12
Male (N, %)	3 (43%)	6 (38%)	1.2 (0.1,10.5)	1
IL-1 or IL-6 blockade (N, %)	7 (100%)	15 (94%)	Inf (0.0,Inf)	1
MAS (N, %)	5 (71%)	2 (13%)	14.5 (1.4, 266.7)	0.01
Eosinophilia (N, %)	5 (71%)	8 (50%)	2.4 (0.3,32.5)	0.41
Trisomy 21 (N, %)	0 (0%)	3 (19%)	0.0 (0.0,5.7)	0.53
History of drug reaction (N, %)	6 (86%)	6 (38%)	9.0 (0.8,503.1)	0.07

SJIA = systemic juvenile idiopathic arthritis; MAS = macrophage activation syndrome.

For age at diagnosis effect size is mean difference, for all other variables effect size is odds ratio.

Odds ratio above 1 indicates the given variable is more likely in SJIA-LD.

Table 2

Characteristics of 86 patients with SJIA, divided by those with eosinophilia or not.

	All patients with SJIA (n=86)	Eosinophilia (n=33)	No eosinophilia (n=53)	Mean difference(CI)	P-value (eosinophilia vs no eosinophilia)
Age at Diagnosis (y) (mean, range)	6.7, (1–16)	6.3, (1–16)	7.0, (1–16)	−0.8 (−2.8, 1.3)	0.47
				Odds ratio (CI)	
Male (N, %)	33 (38%)	13 (39%)	20 (38%)	1.1 (0.4, 2.6)	0.88
IL-1 or IL-6 blockade (N, %)	82 (95%)	32 (97%)	50 (94%)	1.9 (0.2, 103.8)	1
MAS (N, %)	15 (17%)	10 (30%)	5 (9%)	4.1 (1.3, 14.7)	0.01
Lung disease (N, %)	7 (8%)	5 (15%)	2 (4%)	4.5 (0.7, 49.8)	0.1
Trisomy 21 (N, %)	3 (3%)	2 (6%)	1 (2%)	3.3 (0.2, 201.4)	0.56
History of drug reaction (N, %)	18 (21%)	11 (33%)	7 (13%)	3.2 (1.1,10.0)	0.03

SJIA = systemic juvenile idiopathic arthritis; MAS = macrophage activation syndrome.

For age at diagnosis effect size is mean difference, for all other variables effect size is odds ratio.

Odds ratio above 1 indicates the given variable is more likely in patients with eosinophilia.

TABLE 3

Comparison of SJIA patients without lung disease based on DRB1*15:XX status

	SJIA patients without lung disease with HLA DR Typing (n=16)			
	DRB1*15:XX positive (n=10)	**DRB1*15:XX negative (n=6)**	**Mean difference (CI)**	**P-value**
Age at Diagnosis (y)mean, (range)	6.2 (1–16)	9.3 (5–16)	−3.1 (−8.6,2.3)	0.24
			Odds ratio (CI)	
Male N, (%)	4 (40%)	2 (33%)	1.31(0.1, 21.3)	1
IL-1 or IL-6 blockadeN, (%)	9 (90%)	6 (100%)	0 (0,64.9)	1
MAS N, (%)	1 (10%)	1(17%)	0.6 (0.01, 52.55)	1
Eosinophilia N, (%)	5 (50%)	3 (50%)	1 (0.09, 11.69)	1
Trisomy 21 N, (%)	3 (30%)	0 (0%)	Inf (0.25, Inf)	0.25
History of drug reaction N, (%)	3 (30%)	3 (50%)	0.45 (0.03, 5.51)	0.61

For age at diagnosis effect size is mean difference, for all other variables effect size is odds ratio.

Odds ratio above 1 indicates the given variable is more likely in DRB1*15:XX positive.

SJIA = systemic juvenile idiopathic arthritis; MAS = macrophage activation syndrome.

Table 4

Comparison of patients with eosinophilia prior to initiation of anti-IL 1 or anti-IL 6 blockade versus patients with eosinophilia only after initiation of these treatments.

	SJIA patients with complete eosinophilia data (n=28)			
	Eosinophilia before treatment (n=12)	**Eosinophilia only after treatment (n=16)**	**Mean Difference (CI)**	**P-value**
Age	6.67 (1–16)	6.75 (1–16)	−0.08 (−4.4, 4.2)	0.97
			Odds ratio (CI)	
Male (number, %)	5 (42%)	6 (38%)	1.18 (0.2, 7.0)	1
MAS (number, %)	4 (33%)	6 (38%)	0.84 (0.1, 5.1)	1
Trisomy 21 (number, %)	1 (8%)	1 (6%)	1.35 (0.0, 114.0)	1
History of drug reaction (number, %)	4 (33%)	6 (38%)	0.84 (0.1, 5.1)	1
HLA DRB1*15:XX positive (number, %)	4 (10%)	5 (6%)	Inf (0.2, Inf)	0.49
Lung disease	2 (17%)	2 (12%)	1.38 (0.1,22.2)	1

For age at diagnosis effect size is mean difference, for all other variables effect size is odds ratio.

Odds ratio above 1 indicates the given variable is more likely in those with eosinophilia before treatment.