BRIEF REPORT

Impact of IL1RN Variants on Response to Interleukin-1 Blocking Therapy in Systemic Juvenile Idiopathic Arthritis

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Objective. To analyze the reported association of IL1RN polymorphisms with response to interleukin-1 (IL-1) blockade in a German cohort of patients with systemic juvenile idiopathic arthritis (JIA), and to assess the impact of other factors on treatment response.

Methods. Sixty-one patients with systemic JIA who had received IL-1 blockade were identified within the German Autoinflammatory Disease registry DNA biobank. Response to IL-1 blockade was assessed according to 1) the clinical response (initially at least a transient response or good response compared to a poor response), 2) switch (or no switch) to anti–IL-6 receptor therapy following IL-1 blockade, 3) achievement of clinically inactive disease within 6 months of IL-1 blockade, 4) improvement in disease activity measured using the modified Juvenile Arthritis Disease Activity Score, and 5) achievement of a glucocorticoid-free state. In addition, basic demographic data, key features of the disease course, laboratory data, and IL1RN single-nucleotide polymorphisms (SNPs) were assessed.

Results. Six of 7 IL1RN SNPs reported to be associated with response to anakinra therapy were analyzed. These 6 IL1RN SNPs were inherited as haplotypes. An association of IL1RN haplotypes and SNPs with response to IL-1 blockade could not be confirmed in this cohort of patients with systemic JIA. Patients who received tocilizumab following IL-1 blockade had a longer duration from disease onset to diagnosis than those who did not receive tocilizumab (median 0.27 years versus 0.08 years).

Conclusion. The results of this study could not confirm an impact of IL1RN SNPs on response to IL-1 blockade therapy with either anakinra or canakinumab in a cohort of patients with systemic JIA. However, a longer time frame from disease onset to diagnosis was associated with poorer long-term treatment response, thereby supporting the “window of opportunity” hypothesis that suggests improved long-term treatment response with shorter time from disease onset to diagnosis (and treatment).

INTRODUCTION

Systemic juvenile idiopathic arthritis (JIA) is characterized by systemic inflammation and arthritis (1). While, traditionally, glucocorticoids have been an important treatment option for systemic JIA, more recently, cytokine-directed therapies targeting interleukin-1 (IL-1) and IL-6 have also been employed (2). Currently, 3 biologic agents are approved for the treatment of systemic JIA in the European Union: anakinra, a recombinant IL-1 receptor antagonist (IL-1Ra), canakinumab, a human monoclonal IL-1β antibody, and tocilizumab, a humanized monoclonal IL-6 receptor antibody (in the US, only canakinumab and tocilizumab are approved).

The treatment response to IL-1 blockade is heterogeneous. For example, in a randomized, controlled clinical trial of anakinra...
in patients with active systemic JIA, ~71% of patients were considered to be responders, according to achievement of the American College of Rheumatology (ACR) Pediatric 30 (Pedi 30) response (3), resolution of fever, and improvement by 50% in the levels of inflammation markers (4). In a randomized, controlled trial of canakinumab, 84% of patients reached a modified ACR Pedi 30 response within 2 weeks of therapy (5). The response rates reported from open-label cohort studies are variable, but are generally in the range of 75–85% (6,7). The reason for the heterogeneity of response to IL-1 blockade is unclear. One hypothesis is that a “window of opportunity” exists, meaning that there is a time frame early in the disease course during which effective therapy may fundamentally improve the long-term outcome and disease course, essentially suggesting that earlier therapy may be associated with an improved treatment response (8). More recently, it was suggested that high-expressing IL1RN alleles are associated with a higher risk of nonresponse to anakinra therapy in a cohort of North American patients with systemic JIA (9). The IL1RN gene encodes the endogenous IL-1Ra, of which anakinra is a modified version (N2-L-methionyl-26-177–IL-1Ra).

In this study, we analyzed the relationship between treatment response to IL-1 blockade and IL1RN variants in a cohort of patients with systemic JIA identified from the DNA biobank of the German Autoinflammatory Disease (AID) registry.

PATIENTS AND METHODS

Patients. The German AID registry and biobank, comprising data from a total of 42 participating centers, enrolled patients with various autoinflammatory diseases, including systemic JIA. Enrollment into the AID registry was based on clinicians’ diagnoses and could take place at any time during the disease course. For this study, the biobank was screened for patients who were diagnosed as having systemic JIA (n = 177 in total); among these patients, we identified those who had received anakinra and/or canakinumab during the course of their disease (n = 92 remaining), and then identified those who had a DNA sample available (n = 61 remaining).

Assessment of treatment response. The German AID registry includes detailed longitudinal records of individual patients concerning disease activity and laboratory findings. The main outcome of the study was the treatment response, which was assessed according to 2 different parameters: 1) formal assessment of the clinical response, and 2) patterns of treatment with biologic agents.

The clinical response in patients with systemic JIA was formally assessed according to the following response categories: 1) a good response, if the signs and symptoms of active disease (fever, rash, adenopathy, hepatosplenomegaly, serositis, and arthritis) had resolved and if the levels of inflammation markers (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) had improved by at least 50% following treatment with anakinra and/or canakinumab, and if this response was maintained for at least 6 months; 2) a transient response, if there was an initial response characterized according to the parameters of a good response for at least 2 months but with later recurrence of disease; or 3) a poor response, if the parameters for improvement were not met. These treatment response criteria had been previously established for the purpose of a separate analysis of the AID registry cohort (10).

Treatment response based on treatment patterns was judged as follows. Patients who initiated treatment with tocilizumab following either anakinra and/or canakinumab therapy were classified into 1 treatment pattern group, and patients who did not receive tocilizumab following anakinra and/or canakinumab therapy were classified into the other treatment pattern group. This approach estimates the drug survival that was supposed to reflect the long-term efficacy of treatment with anakinra and/or canakinumab, essentially a measure of patients “voting with their feet.”

For secondary analyses, we used the following additional improvement criteria: 1) any response, i.e., improvement of fever (if present) and/or arthritis (if present), defined according to the criteria used by Arthur et al (9), 2) improvement in the physician global assessment of disease activity score by at least 50%, 50%, 70%, or 90%, 3) improvement in the modified Juvenile Arthritis Disease Activity Score in 10 joints (JADAS-10), consisting of the sum of the physician global assessment of disease activity score (scale 0–10), the count of joints with active arthritis (scale 0–10), and normalized CRP level (scale 0–10; calculated as [CRP (in mg/liter) – 10]/10, with a CRP level of <10 mg/liter representing a score of 0), 4) development of clinically inactive disease (CID) within 6 months of initiation of IL-1 blockade, defined according to the CID criteria of a physician global assessment of disease activity score of 0 (scale of 0–10), a CRP level or ESR within the normal range, and no documentation of active arthritis, fever, rash, adenopathy, hepatosplenomegaly due to systemic JIA, uveitis, or morning stiffness, and 5) attainment of a glucocorticoid-free state within 6 months of initiation of IL-1 blockade (11,12).

Genotyping. SNP genotyping was performed in the Core Facility Genomics of the University of Munster, assessing the following SNPs in the IL1RN gene (with indication of the high-expressing allele in parentheses): rs55663133 (−), rs62158854 (T), rs62158853 (C), rs55709272 (T), rs7580634 (G), rs4251961 (T), and rs55942804/rs555447483 (−). However, the SNP rs55942804/rs555447483, which was also reported by Arthur et al (9), could not be genotyped due to technical issues.

Biomarker analysis. Within the biobank of the AID registry, the serum biomarkers S100A8/A9 and S100A12 were routinely assessed. In addition, the biobank was queried, and
| Characteristic                                      | All patients (n = 61) | At least transient response (n = 41) | Poor response (n = 16) | No subsequent switch to TCZ (n = 41) | Subsequent switch to TCZ (n = 20) | P       |
|---------------------------------------------------|-----------------------|--------------------------------------|------------------------|-------------------------------------|-----------------------------------|---------|
| Female/male, no. (%)                              | 25 (41)/36 (59)       | 18 (44)/23 (56)                      | 6 (38)/10 (62)         | 17 (41)/24 (59)                     | 8 (40)/12 (60)                    | 0.91    |
| Age at disease onset, years                       | 5.2 (0.5–17.3)        | 5.6 (0.5–17.3)                      | 5.1 (0.6–12.9)         | 5.6 (0.6–17.3)                     | 4.9 (0.5–12.9)                    | 0.11    |
| Age at diagnosis, years                           | 5.3 (0.5–17.4)        | 7.0 (0.5–17.4)                      | 5.3 (0.0–16.6)         | 7.0 (0.7–17.4)                     | 4.9 (0.5–16.6)                    | 0.22    |
| Onset to diagnosis, years                         | 0.09 (0.0–10.6)       | 0.09 (0.0–3.2)                      | 0.12 (0.01–10.6)       | 0.08 (0.0–3.2)                     | 0.27 (0.0–10.6)                    | 0.02    |
| Onset to final follow-up, years                   | 5.7 (0.7–27.4)        | 4.3 (0.7–17.7)                      | 8.6 (0.9–24.0)         | 3.5 (0.7–27.4)                     | 7.5 (0.9–24.0)                    | <0.01   |
| Pattern of joint involvement, no. (%)             |                       |                                      |                        | 0.08†                               | 0.76†                             |         |
| None                                              | 6 (9.8)               | 6 (14.6)                             | 0 (0.0)                | 4 (9.8)                             | 2 (10.0)                          |         |
| Arthralgia                                        | 12 (19.7)             | 10 (24.4)                            | 1 (6.3)                | 9 (22.0)                            | 3 (15.0)                          |         |
| Oligoarthritis                                    | 7 (11.5)              | 5 (12.2)                             | 2 (12.5)               | 5 (12.2)                            | 2 (10.0)                          |         |
| Polyarthritis                                     | 34 (55.7)             | 19 (46.3)                            | 13 (81.3)              | 22 (53.7)                           | 12 (60.0)                         |         |
| Maximum recorded WBC count, × 10^9/liter          | 173 (5.1–53.5)        | 245.9 (9.8–48.8)                     | 23.4 (10.1–53.5)       | 25.6 (9.8–48.8)                     | 26.3 (10.1–53.5)                  | 0.16    |
| Minimum recorded Hgb level, gm/dl                 | 119 (5–14.6)          | 119 (9.2–14.9)                       | 120 (9.9–15.3)         | 119 (8.2–14.9)                      | 120 (9.6–15.3)                    | 0.85    |
| Maximum recorded CRP level, mg/liter              | 138.5 (1.0–930.0)     | 150.7 (9.4–930.0)                    | 163.7                  | 143.2 (15.0–302.8)                  | 143.2 (15.0–302.8)                | 0.03    |
| Maximum recorded ESR, mm/hour                     | 80 (4–143)            | 77 (6–143)                           | 117 (4–135)            | 77 (5–125)                          | 99 (4–143)                        | 0.05    |
| Maximum recorded S100A8/A9 level, ng/ml           | 2.565 (200–45.390)    | 2.940 (200–45.390)                   | 1.520 (490–12,050)     | 2.580 (200–29,230)                  | 2.940 (490–45,390)                | 0.84    |
| Maximum recorded S100A12 level, ng/ml             | 450 (14–22,730)       | 2,160 (47–22,730)                    | 340 (76–1,470)         | 2,160 (47–22,730)                   | 450 (76–17,850)                   | 0.66    |
| Modified JADAS-10 score at initiation of IL-1 blockade†| 17.0 (5.0–30.0)   | 15.5 (10.0–28.0)                     | 20.1 (13.0–30.0)       | 14.8 (5–29)                         | 20.1 (13–30)                      | 0.06    |
| On glucocorticoid therapy at initiation of IL-1 blockade, no. (%) | 49 (80.3)              | 34 (82.9)                           | 13 (81.3)              | 32 (87.0)                           | 17 (85.0)                          | 0.52    |
| Prednisone-equivalent dose at time of initiation of IL-1 blockade, mg/kg | 0.17 (0.0–15)       | 0.20 (0.0–15)                       | 0.18 (0.0–10)          | 0.15 (0.0–15)                      | 0.22 (0.0–2)                      | 0.43    |
| Off glucocorticoid therapy within 6 months of IL-1 blockade, no./total (%) | 25/49 (51.0)          | 19/34 (55.9)                        | 5/13 (38.4)            | 20/33 (60.6)                       | 5/16 (31.3)                       | 0.05    |
| Prednisone-equivalent dose at time of discontinuation of glucocorticoid, mg/kg | 0.00 (0.00–0.77)     | 0.00 (0.00–0.40)                     | 0.13 (0.00–0.77)       | 0.06 (0.00–0.20)                    | 0.15 (0.00–0.77)                   | <0.01   |
| Biologic treatment, no. (%)                       | ND                    | ND                                   |                       | ND                                  | ND                                 |         |
| Anakinra                                          | 57 (93.4)             | 39 (95.1)                            | 16 (100.0)             | 37 (90.2)                           | 20 (100.0)                        |         |
| Canakinumab                                       | 15 (24.6)             | 9 (22.0)                             | 4 (25.0)               | 9 (22.2)                            | 6 (30.0)                          |         |
| Anakinra and canakinumab                          | 11 (18.0)             | 7 (17.1)                             | 4 (25.0)               | 5 (12.2)                            | 6 (30.0)                          |         |
| Any TCZ                                           | 23 (37.7)             | 10 (24.4)                            | 13 (81.3)              | 3 (73)                              | 20 (100.0)                        |         |
| TCZ after IL-1 blockade                           | 20 (32.8)             | 7 (17.1)                             | 13 (81.3)              | 0 (0.0)                             | 20 (100.0)                        |         |

* Except where indicated otherwise, values are the median (range). P values were determined by Mann-Whitney U test for continuous variables and by chi-square test for categorical variables. TCZ = tocilizumab; WBC = white blood cell; Hgb = hemoglobin; ESR = erythrocyte sedimentation rate; IL-1 = interleukin-1; ND = not determined. † P for trend. ‡ The Juvenile Arthritis Disease Activity Score in 10 joints (JADAS-10) is the sum of the physician global assessment of disease activity score (scale 0–10), count of joints with active arthritis (scale 0–10), and normalized C-reactive protein (CRP) level (scale 0–10; calculated as [CRP (in mg/liter) − 10]/10, with a CRP level <10 mg/liter representing a score of 0).
for each of the patients in this cohort, at least 2 additional serum samples were examined. Many of the patients had a large number of serum samples stored within the AID registry biobank (up to 60 serum samples). For all of the available serum samples, the levels of S100A12, a calgranulin that shows a strong correlation with disease activity in systemic JIA (13,14), had already been recorded. In order to achieve some degree of standardization for each patient, the serum sample with the highest S100A12 level and the serum sample with lowest S100A12 level, supposedly reflecting the highest and lowest overall inflammatory activity, respectively, for that individual patient were examined. Luminex multiplex analysis of the following cytokines was performed: CXCL9, IL-1β, IL-1Ra, IL-6, IL-17A, IL-18, and S100A12.

**Statistical analysis.** Descriptive statistics concerning the relationship between the various clinical parameters and treatment response were calculated. The relationship between the different IL1RN homozygous polymorphisms and treatment response was assessed using the chi-square test. Receiver operating characteristic (ROC) curve analysis was performed to assess the accuracy of the continuous variables regarding outcomes. A plot of linkage disequilibrium was prepared using the Haploview software package (Broad Institute of MIT and Harvard).

**RESULTS**

**Patient characteristics and treatment responses.** The patient cohort consisted of 61 patients who were treated with anakinra and/or canakinumab during the course of their disease; 57 (93.4%) of 61 patients had received anakinra, 15 (24.6%) had received canakinumab, and 11 (18.0%) had received both. Of the 61 patients, 41 (67%) showed at least a transient clinical response and 16 (26%) had a poor clinical response, while for 4 patients (7%), an assessment of the clinical response was not available. Twenty-three patients had received/switched to tocilizumab, including 20 (33%) who switched following prior therapy with anakinra and/or canakinumab, and 3 who switched prior to receiving anakinra and/or canakinumab, meaning that 41 patients (67%) had not switched to tocilizumab following the initiation of IL-1 blockade (Table 1). The treatment responses in these 2 groups overlapped to some degree, as indicated by the distribution of treatment responses in Table 2.

Analysis of the basic characteristics indicated that patients who did not experience a switch to tocilizumab had a lower duration from disease onset to diagnosis than those who had to later switch to tocilizumab (median 0.08 years compared to 0.27 years; \( P = 0.02 \)). ROC curve analysis of the duration from disease onset to diagnosis and future switch to tocilizumab showed an area under the ROC curve of 0.69 (95% confidence interval 0.54–0.83). Furthermore, there were differences concerning the total duration of follow-up between these 2 response groups (median follow-up

| Treatment response                        | No. of responders based on lack of subsequent tocilizumab therapy | No. of nonresponders based on subsequent tocilizumab therapy | Total no. |
|-------------------------------------------|------------------------------------------------------------------|-----------------------------------------------------------|----------|
| Clinical response†                        |                                                                  |                                                           |          |
| Good                                      | 33                                                               | 4                                                         | 37       |
| Transient                                 | 1                                                                | 3                                                         | 4        |
| Poor/absent                               | 3                                                                | 13                                                       | 16       |
| Not classifiable                          | 4                                                                | 0                                                         | 4        |
| Any response‡                             |                                                                  |                                                           |          |
| Yes                                       | 39                                                               | 11                                                       | 50       |
| No                                        | 1                                                                | 9                                                         | 10       |
| Not classifiable                          | 1                                                                | 0                                                         | 1        |
| PGA30 within 6 months                     |                                                                  |                                                           |          |
| Yes                                       | 27                                                               | 12                                                       | 39       |
| No                                        | 4                                                                | 7                                                         | 11       |
| Not classifiable                          | 10                                                               | 1                                                         | 11       |
| PGA50 within 6 months                     |                                                                  |                                                           |          |
| Yes                                       | 27                                                               | 8                                                         | 35       |
| No                                        | 4                                                                | 11                                                       | 15       |
| Not classifiable                          | 10                                                               | 1                                                         | 11       |
| PGA70 within 6 months                     |                                                                  |                                                           |          |
| Yes                                       | 21                                                               | 6                                                         | 27       |
| No                                        | 10                                                               | 13                                                       | 23       |
| Not classifiable                          | 10                                                               | 1                                                         | 11       |
| PGA90 within 6 months                     |                                                                  |                                                           |          |
| Yes                                       | 14                                                               | 3                                                         | 17       |
| No                                        | 17                                                               | 16                                                       | 33       |
| Not classifiable                          | 10                                                               | 1                                                         | 11       |
| Modified JADAS-10 score ≤5 within 6 months|                                                                  |                                                           |          |
| Yes                                       | 14                                                               | 1                                                         | 15       |
| No                                        | 6                                                                | 15                                                       | 21       |
| Not classifiable                          | 21                                                               | 4                                                         | 25       |
| CID within 6 months                       |                                                                  |                                                           |          |
| Yes                                       | 17                                                               | 2                                                         | 19       |
| No                                        | 22                                                               | 17                                                       | 39       |
| Not classifiable                          | 2                                                                | 1                                                         | 3        |
| Off glucocorticoid therapy within 6 months|                                                                  |                                                           |          |
| Yes                                       | 20                                                               | 5                                                         | 25       |
| No                                        | 13                                                               | 11                                                       | 24       |
| Not classifiable                          | 8                                                                | 4                                                         | 12       |

* PGA30 = 30% improvement in the physician global assessment of disease activity score; JADAS-10 = Juvenile Arthritis Disease Activity Score in 10 joints; CID = clinically inactive disease.
† A good response was defined as the resolution of signs and symptoms of active disease (fever, rash, adenopathy, hepatosplenomegaly, serositis, and arthritis) and improvement by at least 50% in the levels of inflammation markers (C-reactive protein and erythrocyte sedimentation rate).
‡ Defined as improvement in fever (if present) and/or arthritis (if present).
IL1RN polymorphisms and response to IL-1Ra blockade

In addition, the maximum recorded CRP and ESR values were higher in patients who later switched to tocilizumab than in those who did not switch (median CRP 143 mg/liter versus 74 mg/liter; median ESR 99 mm/hour versus 77 mm/hour). Other parameters, including sex, age at onset, age at diagnosis, proportion of patients treated with glucocorticoids, and the median dose of glucocorticoids at initiation of IL-1 blockade, maximum recorded white blood cell count, minimum recorded hemoglobin level, and maximum recorded S100A8/A9 and S100A12 protein levels were not different between the response groups.

**IL1RN haplotypes and treatment responses.** Six previously reported SNPs in the **IL1RN** gene were genotyped. Genotyping of the rs55663133, rs62158853, rs62158854, rs55709272, rs7580634, and rs4251961 SNPs was successful in 55 patients (90.1%), 54 patients (88.5%), 57 patients (93.4%), 60 patients (98.3%), 58 patients (95.0%), and 61 patients (100%), respectively. We observed that there was strong linkage disequilibrium (see Supplementary Figure 1, available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41130/abstract), suggesting that the SNPs were present as haplotypes, i.e., either homozygous (n = 22 [36.1%]), heterozygous (n = 32 [52.5%]), or null (n = 7 [11.5%]) for the target genotypes.

We pursued analyses comparing the frequencies of the different genotypes across different outcomes, including 1) clinical response, 2) subsequent switch (or no switch) to tocilizumab, 3) improvement in the physician global assessment of disease activity score by at least 30%, 50%, 70%, and 90%, 4) achievement of a modified JADAS-10 score of 5 or better within 6 months of IL-1 blockade, 5) achievement of CID within 6 months of IL-1 blockade, and 6) attainment of a glucocorticoid-free state (Table 3 and Supplementary Table 1, available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41130/abstract). None of these outcomes was associated with the IL1RN haplotype.

**IL1RN alleles and treatment responses.** When the proportions of the individual effect alleles between the key outcomes were analyzed, similar to that in the analysis by Arthur et al. (9), the frequencies were not different between patients with systemic JIA who demonstrated at least a transient response to IL-1 blockade and those who experienced either a poor or absent response (see Supplementary Table 2 at http://onlinelibrary.wiley.com/doi/10.1002/art.41130/abstract). A different grouping, i.e., comparing patients with a good clinical response to those with only a transient or poor response, did not yield significant differences in individual effect allele frequencies (see Supplementary Table 3 at http://onlinelibrary.wiley.com/doi/10.1002/art.41130/abstract). There were also no significant differences in individual effect allele frequencies when response was evaluated according to the second outcome measure, i.e., patients who received tocilizumab following anakinra and/or canakinumab therapy versus those who did not. Furthermore, the findings did not differ when assessed according to those patients who had received IL-1 blockade with anakinra only (and not with canakinumab) (see Supplementary Table 4 at http://onlinelibrary.wiley.com/doi/10.1002/art.41130/abstract).

Table 3. **IL1RN** haplotypes in patients with systemic juvenile idiopathic arthritis and relationship to clinical treatment responses*

| Haplotype, no./total (%) | Patients with available data, no. |
|-------------------------|----------------------------------|
|                         | Homozygous | Heterozygous | Null |
| Clinical response        |           |             |      |
| At least transient       | 57        | 15/21 (71.4) | 22/31 (71.0) | 4/5 (80.0) |
| Good                     | 57        | 13/21 (61.9) | 20/31 (64.5) | 4/5 (80.0) |
| No switch to tocilizumab | 61        | 13/22 (59.1) | 22/32 (68.8) | 6/7 (85.7) |
| Any response†            | 60        | 18/22 (81.8) | 27/32 (84.4) | 5/6 (83.3) |
| Physician global assessment score by at least 30% within 6 months of IL-1 blockade | 50 | 11/16 (68.8) | 26/30 (86.7) | 2/4 (50) |
| Improved at least 50%    | 50        | 9/16 (56.3)  | 24/30 (80.0) | 2/4 (50) |
| Improved at least 70%    | 50        | 8/16 (50)    | 17/30 (56.7) | 2/4 (50) |
| Improved at least 90%    | 50        | 6/16 (38)    | 11/30 (36.7) | 0/4 (0)  |
| Best modified JADAS-10 score ≤5 within 6 months of IL-1 blockade‡ | 36 | 5/12 (42) | 7/20 (35) | 3/4 (75) |
| CID within 6 months of IL-1 blockade | 58 | 9/21 (42.9) | 9/31 (29.0) | 1/6 (16.7) |
| Off glucocorticoid therapy within 6 months of IL-1 blockade | 49 | 11/18 (61.1) | 11/27 (40.7) | 3/4 (75.0) |

* Differences between the haplotypes (P values by chi-square test) were not significant for any response group.
† Defined as improvement in fever (if present) and/or arthritis (if present).
‡ The Juvenile Arthritis Disease Activity Score in 10 joints (JADAS-10) is the sum of physician global assessment of disease activity score (scale 0–10), count of joints with active arthritis (scale 0–10), and normalized C-reactive protein level (scale 0–10; calculated as [CRP (in mg/liter) – 10]/10, with a CRP level <10 mg/liter representing a score of 0).
Serum biomarkers and treatment responses. The comparison of several serum biomarkers obtained from the biobank sample with the highest serum S100A12 level for each individual patient demonstrated that only the IL-1Ra level was different between the different response groups. In analyses with treatment response defined as at least a transient clinical response or according to a treatment pattern of not switching to tocilizumab, those who were designated as responders had higher serum IL-1Ra levels (see Supplementary Table 5 at http://onlinelibrary.wiley.com/doi/10.1002/art.41130/abstract). The other biomarkers measured did not differ between the response groups.

Further analysis of nonparametric correlations between the different biomarkers across all samples tested indicated a substantial degree of correlation between the levels of most of the biomarkers, but not for IL-1Ra (see Supplementary Figure 2 at http://onlinelibrary.wiley.com/doi/10.1002/art.41130/abstract). Subsequently, the database was further queried in order to determine whether patients were receiving anakinra therapy at the time of serum sampling. Indeed, many of the patients were receiving anakinra at the time of sampling. Measured IL-1Ra serum levels were, on average, approximately an order of magnitude higher in patients receiving anakinra therapy (see Supplementary Figure 3 at http://onlinelibrary.wiley.com/doi/10.1002/art.41130/abstract), indicating that the measured IL-1Ra levels likely represent the presence of anakinra, i.e., recombinant IL-1Ra. Assessment of IL-1Ra serum levels measured both in the individual samples with the highest S100A12 serum levels and in those with the lowest S100A12 serum levels did not demonstrate any correlation with the different IL1RN haplotypes (data not shown).

DISCUSSION

In this real-world cohort of well-characterized German patients with systemic JIA who had received IL-1 blockade with anakinra and/or canakinumab, we cannot confirm an association of 6 IL1RN gene polymorphisms or the IL1RN haplotype with various definitions of an adequate treatment response. Such an association was previously reported by Arthur et al for 7 IL1RN gene polymorphisms in a small cohort of US patients with systemic JIA who had received anakinra therapy (9). Although we were unable to genotype 1 of the reported 7 SNPs (rs55942804/rs555447483) due to technical issues, we do not believe that this had an impact on our conclusions, the reason being that this SNP generally is part of the same strongly conserved haplotype as the other 6 SNPs. The data previously presented by Arthur et al (9) support a compelling hypothesis. On the one hand, higher-expressing IL1RN alleles, i.e., higher endogenous IL-1Ra production, may be associated with a lower risk of developing systemic JIA. On the other hand, once systemic JIA is present, it carries a higher risk of nonresponse to treatment with anakinra (recombinant IL-1Ra).

It is unclear as to why such an association was not seen in this German cohort. Interestingly, whereas an association of the different IL1RN SNPs with risk of systemic JIA was seen in several of the systemic JIA cohorts (from the US, UK, Turkey, Italy, Brazil, Argentina, Canada, and Spain) reported by Arthur et al (9), most prominently, for rs55663133, we did not observe any association in the German cohort. Therefore, it is possible that genetic risk factors for systemic JIA and for treatment nonresponse vary in different populations. Clearly, systemic JIA is very heterogeneous, both genetically—for example, ranging from a rather benign condition with a monophasic disease course to a serious condition with chronic destructive arthritis or complicated by life-threatening macrophage activation syndrome—and genetically, as outlined by Arthur et al (9).

In the cohort described in the study by Arthur et al, the patients were not characterized in more detail, so that further comparisons with our cohort are not feasible. Furthermore, whereas 38 patients were evaluated in the study by Arthur et al (9), the cohort was somewhat larger, comprising 61 patients, in the present study.

Considering other potential predictors of nonresponse to therapy with IL-1 blockade, there is some indication that patients with a long-term nonresponse, based on a subsequent switch to IL-6 blockade with tocilizumab, have a longer duration from onset of symptoms to diagnosis when compared to those with a persistent response (median 0.27 years compared to 0.08 years). This observation supports the “window of opportunity” hypothesis, i.e., early diagnosis and treatment may positively influence the long-term outcome of the disease (8). However, we did not observe a significant association of duration from onset to diagnosis and a different measure of treatment response (clinical response).

While we attempted to correlate serum IL1Ra levels with 1) the different IL1RN SNPs, and 2) treatment response, this was fraught with difficulty. First, an association of the different SNPs with serum IL-1Ra levels was not observed. Second, while higher IL-1Ra serum levels were detected, this was most likely attributable to the ongoing treatment with anakinra in these patients, since the assay used does not distinguish between the endogenous IL-1Ra and anakinra (N2-L-methionyl-26-177–IL-1Ra), i.e., the analyte of interest represents the active treatment that was given to many of the patients.

Our study has several limitations. Some of the patients had a disease onset after the age of 16 years, and therefore they did not fulfill the International League of Associations for Rheumatology criteria for systemic JIA (15). However, these criteria are a subject of controversy, and potentially more appropriate criteria have been suggested (16,17). The present study focuses on a cohort of patients with variable duration of follow-up, which may have an impact on the treatment outcomes; for example, a patient with a much longer disease course may have a higher chance to receive tocilizumab following IL-1 blockade. We were unable to extract more formal response criteria from the registry, such as the modified ACR Pedi 30 response criteria or the complete JADAS criteria, each of which have been used in controlled clinical trials. This was because some of the criteria, such as patient global assessment of disease activity (5), were not recorded.
Nevertheless, from a clinical standpoint, we believe that our assessment of treatment response, i.e., clinical response concerning systemic inflammation and drug survival, was valid. Because patients were often not enrolled in the registry early during the disease, the laboratory data recorded in the registry almost certainly do not represent the most prominent changes, since such data are often present at the onset of disease; therefore, conclusions on the impact of certain laboratory abnormalities on treatment outcomes are very limited. Furthermore, assessment of serum cytokine levels, including IL-1Ra, is presumably strongly influenced by multiple factors, such as degree of systemic inflammation and current medications (18), for which we did not control; therefore, based on our current data, it would not be possible to draw conclusions on the effect of IL1RN SNPs on IL-1Ra expression. It would be desirable to extend genetic studies to cohorts that could be better characterized and prospectively followed up.

In summary, despite the limitations mentioned, in this German cohort of patients with systemic JIA treated with IL-1 blockade, we could not find any evidence of an impact of IL1RN SNPs on treatment response to IL-1 blockade. In contrast, this study provides evidence of a “window of opportunity” in this cohort, i.e., improved long-term treatment response with shorter time from disease onset to diagnosis (and treatment, presumably).

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Hinze had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Hinze, Foell.

Acquisition of data. Hinze, Fuehrer, Kessel, Wittkowski, Lainka, Baehr, Hügle, Haas, Ganser, Weißbarth-Riedel, Jansson, Foell.

Analysis and interpretation of data. Hinze, Kessel, Wittkowski, Lainka, Foell.

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