CANAKINUMAB IN SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS: REAL-LIFE DATA FROM A RETROSPECTIVE ITALIAN COHORT

Running head: Canakinumab in a cohort of Italian sJIA patients

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CANAKINUMAB IN A COHORT OF ITALIAN sJIA PATIENTS

ABSTRACT

Objective: To evaluate in real-life the effectiveness and safety of canakinumab in Italian patients with systemic juvenile idiopathic arthritis (sJIA).

Methods: A retrospective multicenter study of children with sJIA was performed. Clinical features, laboratory parameters and adverse events were collected at baseline, after 6 and 12 months from starting canakinumab. The effectiveness primary outcome was clinical inactive disease (CID) off glucocorticoids (GCs) treatment at 6 months.

Results: A total of 80 children were analyzed from 15 Italian centers. Of the 12 patients who started canakinumab in CID while receiving anakinra, all maintained CID. Of the 68 with active disease at baseline, 57.4% achieved CID off GCs at 6 months and 63.8% at 12 months. In univariate analysis, the variables significantly related with non-response were number of active joints (NAJ) ≥5, history of macrophage activation syndrome (MAS) and disease duration. Multivariate analysis confirmed the association with non-response of NAJ ≥5 (OR 6.37 (95%CI 1.69-24.02), p=0.006) and history of MAS (OR 3.53 (95%CI 1.06-11.70), p=0.039). No serious adverse events were recorded in this series. There were two cases of MAS during canakinumab, leading to a rate of 2.9 episodes per 100 patient year.

Conclusion: We confirm, in real-life, the efficacy of canakinumab in sJIA in a multicentric cohort. History of MAS and higher NAJ were associated with lower probability of achieving clinical inactive disease.

Key words: Systemic juvenile idiopathic arthritis, canakinumab, clinical inactive disease

Key messages:

- In real life canakinumab is effective for sJIA patients.
- History of MAS and higher NAJ are associated with lower response to canakinumab.

INTRODUCTION

Systemic juvenile idiopathic arthritis (sJIA) is characterized by chronic arthritis, systemic symptoms, marked elevation of inflammatory markers and absence of autoantibodies [1]. According to International League of Associations for Rheumatology (ILAR), the diagnosis was made by the presence of chronic arthritis associated with daily fever for at least 2 weeks with intermittent rash, lymphadenopathy, hepatomegaly, splenomegaly or serositis [2]. The prevalence of systemic symptoms and the demonstration of a key role of IL-1 and IL-6 in the pathogenesis of the disease, led to consider sJIA an autoinflammatory rather than an autoimmune disease [3]. Treatment with systemic glucocorticoids (GCs) has been commonly used, but with significant side effects. Based on this issue and considering the important role of IL-1 and IL-6 pathways in patients with sJIA, IL-1 and IL-6 inhibitors were successfully used in children with sJIA [4-9]. Several studies confirmed the efficacy of anakinra, a recombinant IL-1 receptor antagonist that blocks both IL1α and IL1β biologic activity in a significant portion of patients with sJIA, especially in the first phase of disease [5, 10-12]. Canakinumab is a fully human, anti-IL1β monoclonal antibody that selectively binds soluble IL-1β, which is overproduced in patients with sJIA [13]. Previous published clinical trials demonstrated the efficacy of canakinumab in sJIA patients in a substantial number of patients [6, 14-17]. In these studies, a consistent percentage of patients were able to withdraw GCs treatment, range from 15.6 to 36.4% [6, 14-17].

To the best of our knowledge, little information is available about the use of canakinumab in real-life in patients with sJIA. Data from German BIKER register on 22 sJIA patients treated with

canakinumab showed an ACR remission in approximately 60% of patients after 24 months of treatment [18]. In this study patients treated with IL-1 inhibitors (anakinra and canakinumab) within 12 months of the disease met clinical remission more frequently than patients who started treatment after the first 12 months [18], according to the hypothesis of window opportunity [19]. In a retrospective study 27 out of 168 (16.1%) sJIA patients were treated with canakinumab due to lack of efficacy or local reaction to anakinra, with clinical and laboratory remission in 85% of them [20].

We describe real-life data with response rates and outcome, as well as safety, in the Italian patients with sJIA treated with canakinumab.

PATIENTS AND METHODS

This is a retrospective, observational, multicenter study of 82 patients with sJIA that started canakinumab before the end of 2019.

All centers of the Italian Pediatric Rheumatology Study Group were asked to make a census of patients with sJIA treated with canakinumab and a collection form has been sent. Medical records of 82 patients with sJIA from 15 Italian pediatric rheumatology centers were retrospectively reviewed: 76 of them reached a follow-up of 6 months. Two patients were excluded from the analysis: one was lost to follow-up up before 6 months and the other developed lymphopenia and withdrew canakinumab. Four patients withdrew canakinumab before 6 months for lack of efficacy, but they were included in the analysis as non-responders. The latter were included in the analysis as non-responders at 6 months.

Clinical and laboratory data were collected in combination with general and demographic data, such as age, gender, age at disease onset, age at starting canakinumab, dosages used, duration of treatment, concomitant and previous treatments, previous macrophage activation syndrome (MAS), and overall adverse events.

Diagnosis of sJIA was established according to ILAR criteria [2]. Data were collected using standardized forms. Demographic data, disease history and baseline (defined as canakinumab initiation) clinical and laboratory features of the patients are included in Table 1. Presence of fever was defined as body temperature above 38°C. Primary outcome was CID at 6 months, according to the preliminary criteria for inactive disease and clinical remission of JIA [21] without glucocorticoids (GCs) treatment.

Normal ranges used for laboratory data were as follows: C-reactive protein (CRP) <0.5 mg/dl, erythrocyte sedimentation rate (ESR) <15 mm/h, ferritin <450 ng/ml, white blood cell count 5500-15000/µl, neutrophil cell count 1650-8250/µl, hemoglobin 10.5-15.5 g/dl and platelet count 150-450 x10^3/µl. The study was approved by the Ethics Committee of the IRCCS Ospedale Pediatrico Bambino Gesù (1683 OPBG 2018). Patients/parents provided written informed consent.

STATISTICAL ANALYSIS

Qualitative variables were expressed as absolute frequency and percentage. Proportions were compared by Chi-square test or Fisher's exact test, as appropriate. Quantitative variables, reported as medians and interquartile ranges (1st and 3rd quartile), were analysed using the Mann-Whitney *U* test for unmatched groups. Association of baseline and disease history variables with the primary outcome (i.e. response defined as CID off GCs) was assessed with univariate analysis. Variables with $p<0.05$ in univariate analysis were included in a logistic regression model having as dependent variable the non-response after 6 months of therapy with canakinumab.

All statistical tests were two sided; a p-value <0.05 was considered as statistically significant. The analyses were performed and graphs generated using Stata 15.1 software (StataCorp LLC, College Station, Texas USA, 2017) and GraphPad Prism 5.0 (GraphPad Software, Inc., San Diego, CA).

RESULTS

Patients

Demographic and laboratory features of the 80 patients analyzed (76 patients with a follow-up of 6 months and 4 patients that withdrew canakinumab before 6 months for lack of efficacy) are summarized in Table 1. At baseline 35 (43.7%) patients were IL-1 inhibitor-naïve and 45 (56.3%) had been previously treated with the IL-1 inhibitor anakinra. Among the patients previously treated with anakinra, 33 (73.3%) discontinued anakinra for lack of efficacy and had active disease (AD) when switched to canakinumab. Twelve (26.7%) patients on anakinra were in CID when switched to canakinumab due to discomfort/pain from daily subcutaneous injections (Table 1). The median age at disease onset was comparable among the three groups. Almost all patients had previously received GCs, while 47.5% of patients had received one or more disease modifying anti-rheumatic drugs (DMARDs) (32.5% methotrexate and 23.8% cyclosporine A) (Table 1).

Among the 68 patients who started canakinumab during AD, 38 (55.9%) had fever. The median number of active joints (NAJ) was 2. It is worth to note that among the patients who started canakinumab after having failed anakinra, 4 of them had failed multiple line of biologics with different mechanisms of action (see footnote in Table 1). The median dose of canakinumab was 4.0 mg/Kg every 4 weeks.

Response at 6 months

After 6 months of canakinumab treatment, 51 patients (63.7%) met criteria for CID off GCs, while 29 patients (36.3%) had AD (14 previously treated with anakinra and 15 biologic naïve) (Figure 1). All 12 patients treated with anakinra who switched to canakinumab, while being in CID off GCs, maintained CID off GCs at 6 months. Of the 33 patients previously treated with anakinra who switched to canakinumab while having AD, 19 (57.6%) patients achieved CID at 6 months, a rate comparable to that of the 20 IL-1 inhibitor-naïve patients (57.1%) (Figure 1).

Univariate analysis of features associated with response

In order to evaluate whether the 6-months response to canakinumab therapy was related to baseline features, we excluded from the analysis the 12 patients who started canakinumab during CID while receiving anakinra. The 68 remaining patients were divided in responders (39/68, 57.4%) and non-responders (29/68, 42.6%) and variables were evaluated in univariate analysis. The four patients who stopped canakinumab for lack of efficacy before 6 months from baseline were considered as non-responders by the treating physicians and therefore considered as non-responders at 6 months in the analysis. As shown in Table 2, no difference was found for the presence of fever at baseline. Notably, a baseline variable significantly related with the response to canakinumab was the NAJ that was higher in the non-responders (p=0.016) (Table 2). Based on the accepted clinical definition of polyarticular JIA, we chose a cut-off of 5 active joints. With this cut-off, we found a statistically significant difference (p=0.001) between non-responders (44.8%) and responders (10.3%) (Table 2).

The risk of non-response after 6 months of therapy with canakinumab among the 17 patients with a NAJ ≥5 at baseline was 2.4 times higher than the risk of non-response among the 51 patients with a NAJ <5 at baseline (risk ratio 2.4 (95%CI 1.5-4.0); p=0.001) (Figure 2A). Responder patients started canakinumab earlier in their disease course than non-responders (p=0.047). History of MAS was significantly more frequent in non-responders (44.8%) than in responders (18.0%) (p=0.016). Patients with a history of MAS presented a risk of non-response 2.0 times higher (95%CI 1.2-3.3) than patients without history of MAS (Figure 2B). All, but one, of the patients receiving cyclosporine at baseline had a history of MAS, and, as expected, cyclosporine treatment was more frequent in non-responders.

Logistic analysis of features associated with response

A logistic regression analysis was performed including NAJ ≥5, history of MAS and disease duration from onset to baseline. Treatment with cyclosporine at baseline was excluded because of collinearity with history of MAS. The full model (pseudo R^2: 0.18) showed that NAJ ≥5 (OR 6.37 (95%CI 1.69-24.02), p=0.006) and history of MAS (OR 3.53 (95%CI 1.06-11.70), p=0.039) remain statistically significant confirming their association with non-response, independently of disease duration (OR 1.00 (95%CI 0.99-1.01), p=0.29) (Table 3). The predicted margins (average predicted response) were calculated to assess the probability of response after 6 months of therapy with canakinumab considering the combination of the two statistically significant variables identified in the logistic model. Patients with a history of MAS and NAJ ≥5 had 11.8% (95%CI 0.0-26.9) probability of response, while patients without a history of MAS and with NAJ <5 had 75.9% (95%CI 62.7-89.0) probability of response (Figure 3).

Response at 12 months

Fifty-seven patients reached a follow up of at least 12 months (Figure 1). Of the 36 patients in CID at 6 months and with follow-up visit at 12 months, 32 (88.9%) maintained CID at 12 months and only 4 (11.1%) flared. Of the 29 patients with active disease at 6 months, 21 reached a follow up of 12 months; 6 (28.6%) of them achieved CID at 12 months. Overall, at 12 months 38/57 patients (66.7%) were in CID off GCs and 19/57 (33.3%) had active disease. When we evaluated the predictive factors identified at 6 months, at 12 months frequency of NAJ≥5 was significantly (p=0.041) higher in non-responders (47.1%) than in responders (16.7%). At 12 months, the difference in history of MAS (responders 16.7%; non –responders 35.3%) showed the same trend, but the difference did not achieve statistical significance (p=0.17), possibly for the smaller sample size.

Safety

No serious adverse events were recorded in this retrospective series. One patient developed lymphopenia that led to withdrawal of canakinumab after 3 months. We observed one patient with a mild injection site reaction, 6 patients with infections, none of them reported as serious, one patient with herpes zoster and one case of transient neutropenia. All resolved with standard treatment and did not require discontinuation of canakinumab. Among the 80 patients, there were two cases of MAS during treatment with canakinumab, leading to a rate of 2.9 MAS episodes per 100 patient year. Both of them developed MAS until 12 months from starting canakinumab and one of them had a previous episode of MAS before starting the therapy.

DISCUSSION

There are no real-life reports on large series of patients with sJIA treated with canakinumab outside of the setting of the controlled trials [6, 14-15]. In our real-life setting we chose to use as primary efficacy outcome the achievement of CID off GCs after 6 months of therapy with canakinumab, according to the criteria proposed by Wallace et al [21]. This primary outcome was used to identify patients with clinically relevant response that combines absence of disease symptoms with withdrawal of glucocorticoids. Indeed, high rate of responses are demonstrated in the trials with canakinumab, as well as with other IL-1 inhibitors in sJIA [10-12, 22]. In our study we found that canakinumab treatment led to CID in approximately 57% of sJIA patients at 6 months and in 67% of those who achieved a 12 months follow-up. This is consistent with what has been reported in a smaller number of patients in a real-life multicentric setting from the BIKER register with approximately 60% (13/22) of sJIA patients achieving persistent CID (ACR remission) after 24 months of treatment [18].

The percentage of CID off GCs found in our study is higher than one reported in clinical trials of Ruperto et al [6, 14, 15], of Nishimura et al [16] and of Brunner et al [17]. A small phase II

multicenter open-label study [14] showed that 15 days after receiving a dose of canakinumab 4 of 25 patients (16.0%) achieved CID. The double-blind trial with 177 sJIA patients showed that, after a median of four injections of canakinumab, 31% of patients met CID criteria [6]. A long-term follow-up (up-to 5 years) of 144/177 patients enrolled in these trials showed that 33% of patients achieved CID at 6 months and 40% at 2 years [15]. The open-label phase III trial with 19 Japanese patients showed that 75% of them achieved CID and 31.3% achieved CID off GCs at 12 months [16]. A prospective open label study on 123 sJIA patients showed that 22% of them met CID (according to the ACR criteria) after 15 days from starting canakinumab and 31% of them met CID at 6 months [17]. This apparent discrepancy with lower rate of CID in clinical trials may be very well explained by different disease severity at baseline, e.g. baseline NAJ was 10.0 in the trials and was 2.0 in our cohort.

Furthermore, in our study we showed that canakinumab maintained CID in those patients who previously achieved it while receiving anakinra. The patients previously treated with anakinra with AD at baseline achieved CID off GCs at 6 months (19/33, 57.6%) with a rate very similar to those who were IL-1 inhibitor naïve (20/35, 57.1%). This observation suggests that failure of one anti-IL1 drug does not necessarily preclude use of another one. The mechanistic implication of our observation remains unclear. Although both anakinra and canakinumab are IL-1 inhibitors, their mechanisms of action are not superimposable: anakinra blocks both IL-1α and IL-1β, while canakinumab binds only to IL-1β. Moreover, these drugs have different pharmacokinetic characteristics. Canakinumab, as expected for monoclonal antibodies targeting soluble molecules, shows linear, dose proportional pharmacokinetics. The effect of anakinra, which is a competitive receptor antagonist, depends on the dose of drug, on the concentration of IL-1, on its competitiveness and on the level of spare receptors [23]. Whether these different features translate into different efficacy in different patients remains unknown.

With the limitation due to the relatively small number of patients, we have analyzed relation of clinical variables with response. We found a trend towards early treatment being associated with better response to canakinumab. This is in line with the finding of the BIKER registry, in which patients who started IL-1 inhibitors within 12 months of disease onset met JADAS remission more frequently than patients who started treatment later [18]. This is also consistent with other experiences with anakinra [12, 24]. Even if formal demonstration of a window of opportunity in a clinical trial is not available, our observation adds to the increasing body of evidence, albeit uncontrolled, that early treatment is associated with better response.

When predictors of lower probability of response were analyzed, we found that a NAJ ≥5 and history of MAS were associated with non-response in univariate and multivariate analysis. This is consistent with some observations [24, 25], but not all, using anakinra in sJIA, although with different cut-off [12]. In our study, patients with a NAJ ≥5 at baseline had a significant higher risk of non-response. As far as history of MAS is concerned, the association with non-response to IL-1 inhibitors has not been reported. However, Hinze et al have recently reported that C-X-C Motif Chemokine Ligand 9 (CXCL9) levels are higher in sJIA patients who did not achieve complete response with canakinumab [26]. CXCL9 is directly related to Interferon-gamma (IFN-γ). Mounting evidence points to a pathogenic role of IFN-γ in MAS, and other hemophagocytic lymphohistiocytosis (HLH) forms [27-29]. In patients with history of MAS we have found higher levels of CXCL9 [27]. Altogether these observations suggest that the biology of patients at risk of MAS may confer lower probability for complete response to canakinumab. Other studies on the immunobiology of sJIA and MAS are needed. The data obtained with predicted margin analysis showed that patients with a history of MAS and NAJ ≥5 had a low probability of response with a 95% confidence interval of 0 to 26.9%. This appears to be of potential clinical relevance in guiding therapeutic decisions, although in a small percentage of patients (in our series there were 7 out of

68, all non-responders). This result needs to be confirmed in a different and possibly larger series of patients with sJIA.

As far as safety of canakinumab is concerned, no serious adverse events were recorded. Adverse events reported were mild injection site reactions, non-serious infections and one case of herpes zoster. None of them required discontinuation of treatment. There was one case of lymphopenia that led to discontinuation of canakinumab before the 6 months of treatment. We observed also one case of neutropenia not associated with infection. No new safety signals were detected compared to what has been reported in clinical trials and from a real-life setting of patients with sJIA treated with canakinumab [6, 14-17, 30]. There were 2 cases of MAS leading to a 2.9 rate per 100 patient year of MAS, superimposable to the rate of 2.8 reported in the canakinumab clinical trials [31].

In addition to the relatively small number of patients, the limitations of our study include also its retrospective nature with no standardization of other treatments. At the same time, this reflects different cares and approaches in different centers making the results relevant to the routine clinical practice.

In conclusion, we confirm in a real-life setting that canakinumab is an effective and safe drug in patients with sJIA. The rate of CID of approximately 60% in this study appears higher than that of clinical trials in which patents with very severe disease were enrolled.

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CANAKINUMAB IN A COHORT OF ITALIAN sJIA PATIENTS

Table 1. Demographic data and baseline characteristics of patients

	All patients (N=80)	IL-1 inhibitor naïve (N=35)	Previous IL-1 inhibitor with AD (N=33)	Previous IL-1 inhibitor in CID (N=12)
Gender, Female[1]	49 (61.3)	22 (62.9)	20 (60.6)	7 (58.3)
Age at disease onset (yrs)[2]	6.5 (3.8-10.6)	7.9 (4.1-11.3)	5.7 (3.0-9.5)	7.1 (4.4-11.4)
Age at treatment start (yrs)[2]	10.4 (6.2-13.4)	10.3 (6.2-12.4)	10.1 (6.1-15.3)	12.3 (9.9-15.3)
Previous treatment				
Glucocorticoids[1]	74 (92.5)	32 (91.4)	32 (97.0)	10 (83.3)
DMARDs				
Methotrexate[1]	26 (32.5)	13 (37.1)	11 (33.3)	2 (16.7)
Cyclosporine[1]	19 (23.8)	7 (20.0)	8 (24.2)	4 (33.3)
bDMARDs[1]	50 (62.5)	5 (14.3)*	33 (100)**	12 (100)***
Previous MAS[1]	26 (32.5)	10 (28.6)	9 (27.3)	7 (58.3)
Time from onset to receiving canakinumab (mo)[2]	20.7 (5.9-48.0)	8.3 (2.8-31.7)	26.3 (10.9-94.5)	31.4 (12.4-83.7)
Baseline features				
Fever (>38.0°C)[1]	38 (47.5)	19 (54.3)	19 (57.6)	0 (0.0)
Rash[1]	26 (32.5)	14 (40.0)	12 (36.4)	0 (0.0)
Number of active joints[2]	0 (0-4)	2 (0-5)	1 (0-4)	0 (0-0)
C-reactive protein (mg/dl)[2]	2.39 (0.33-9.00)	5.45 (0.65-10.83)	2.37 (0.60-13.10)	0.18 (0.07-0.31)
Ferritin (ng/ml)[2]	137 (62-480)	200 (120-909)	165 (73-358)	34 (31-44)
Neutrophil count (x10³/µl)[2]	6.5 (3.5-10.0)	7.2 (5.0-10.4)	5.8 (3.5-8.0)	3.5 (2.6-12.5)
Hemoglobin (g/dl)[2]	11.6 (10.6-12.8)	11.1 (10.4-12.0)	11.4 (10.6-12.5)	13.0 (12.3-13.5)
Platelet count (x10³/µl)[2]	343 (260-473)	397 (280-499)	324 (271-428)	245 (213-331)
Concomitant treatment at baseline:				
Glucocorticoids[1]	54 (67.5)	30 (85.7)	24 (72.7)	0 (0.0)
Dose of GC (mg/Kg/day)[2]	0.5 (0.3-1.0)	0.5 (0.4-1.0)	0.5 (0.3-0.9)	-
DMARDs				
Methotrexate[1]	14 (17.5)	10 (28.6)	3 (9.1)	1 (8.3)
Cyclosporine[1]	10 (12.5)	5 (14.3)	2 (6.1)	3 (25.0)

Canakinumab dose (mg/Kg/4w)[2]	4.0 (3.3-4.0)	4.0 (2.8-4.0)	3.9 (3.7-4.0)	4.0 (3.1-4.0)

Data of all 80 patients and divided in groups based on interleukin-1 (IL-1) inhibitor therapy (naïve or previous therapy) and the state of the disease at the start of canakinumab.

[1] Number (percentage); [2] Median (1st and 3rd quartile)

*1 Etanercept, 4 Tocilizumab; **25 Anakinra, 2 Etanercept + Anakinra, 2 Tocilizumab + Anakinra, 1 Anakinra + Tocilizumab + Adalimumab, 1 Etanercept + Infliximab + Tocilizumab + Anakinra, 1 Infliximab + Golimumab + Tocilizumab + Anakinra, 1 Abatacept + Etanercept + Golimumab + Adalimumab + Tocilizumab + Rituximab + Anakinra; ***10 Anakinra, 1 Anakinra + Tocilizumab; 1 Etanercept + Tocilizumab + Anakinra.

Abbreviations: AD=active disease; CID=clinical inactive disease; DMARDs=Disease Modifying Antirheumatic Drugs; bDMARDs=Biologic Disease Modifying Antirheumatic Drugs; MAS=Macrophage activation syndrome.

Table 2. Univariate analysis for predictors of CID off glucocorticoids at 6 months in patients in AD at baseline.

	RESPONDERS (N=39)	NON-RESPONDERS (N=29)	p-value
Gender, Female[1]	21 (53.9)	21 (72.4)	0.12[C]
Age at disease onset (yrs)[2]	6.1 (3.9-11.1)	6.6 (3.7-9.9)	0.63
Age at treatment start (yrs)[2]	9.9 (6.0-13.3)	10.4 (8.4-15.3)	0.31
Previous treatment with anakinra[1]	19 (48.7)	14 (48.3)	0.97[C]
History of MAS[1]	7 (18.0)	13 (44.8)	0.016[C]
Time from onset to receiving Canakinumab (mo)[2]	13.9 (3.0-33.4)	28.7 (6.9-89.7)	0.047
Baseline features			
Fever (>38.0°C)[1]	22 (56.4)	16 (55.2)	0.92[C]
Rash[1]	16 (41.0)	10 (34.5)	0.58[C]
Number of active joints[2]	1 (0-2)	4 (0-7)	0.016
Active joints ≥5[1]	4 (10.3)	13 (44.8)	0.001[C]
C-reactive protein (mg/dl)[2]	2.70 (0.60-10.83)	5.45 (0.80-13.45)	0.40
Ferritin (ng/ml)[2]	190 (125-480)	133 (77-924)	0.71
Neutrophils count (x10³/μl)[2]	6.2 (4.5-9.3)	7.4 (4.1-12.5)	0.67
Hemoglobin (g/dl)[2]	11.4 (10.5-12.6)	11.1 (10.5-12.2)	0.49
Platelets count (x10³/μl)[2]	355 (280-489)	356 (261-444)	0.57
Concomitant treatment at baseline			
Glucocorticoids[1]	28 (71.8)	26 (89.7)	0.07[C]
Dose of GC (mg/Kg/day)[2]	0.5 (0.4-0.9)	0.6 (0.3-1.0)	0.86
DMARDs			
Methotrexate[1]	5 (12.8)	8 (27.6)	0.13[C]
Cyclosporin[1]	1 (2.6)	6 (20.7)	0.037[F]
Canakinumab dose (mg/Kg/4w)[2]	3.9 (3.5-4.0)	3.9 (3.0-4.0)	0.50

Univariate analysis for predictors of clinical inactive disease (CID) off glucocorticoid (GCs) therapy at 6 months from baseline in patients who started canakinumab with active disease (AD) (n=68).

[1] Number (percentage) – Chi-square test[C]/Fisher's exact test[F]; [2] Median (1st and 3rd quartile) – Mann-Whitney *U* Test

Abbreviations: MAS=Macrophage activation syndrome; DMARDs=Disease Modifying Antirheumatic Drugs.

Table 3. Best-fitting model obtained through logistic regression procedures (Pseudo R^2: 0.18).

Explanatory variable	OR (95% CI)	p[£]
Number of active joints ≥5	6.37 (1.69-24.02)	0.006
History of MAS	3.53 (1.06-11.70)	0.039
Disease duration from onset to baseline	1.00 (0.99-1.01)	0.29

Non-achievement of clinical inactive disease at 6 months from canakinumab start was the dependent variable.

[£]By likelihood ratio test.

Figure 1. Patients' disposition and achievement of clinical inactive disease (CID) off GCs.

Figure 2. Response after 6 months of therapy: relationship with NAJ at baseline (A) and history of MAS (B).

A) Patients with number of active joints (NAJ) <5 at baseline had a significantly better response (68.6% vs 23.5%; chi-square test: p=0.001). Risk ratio of non-response at 6 months of therapy with canakinumab based on NAJ ≥5 was 2.4 (95%CI 1.5-4.0). B) Patients without a history of MAS had a significantly better response (66.7% vs 35.0%; chi-square test: p=0.016). Risk ratio of non-response at 6 months of therapy with canakinumab based on history of MAS was 2.0 (95%CI 1.2-3.3).

Figure 3. Logistic regression analysis of non-achievement of clinical inactive disease at 6 months from starting canakinumab.

Best-fitting model obtained through logistic regression procedures (Pseudo R2: 0.18). Non-achievement of clinical inactive disease at 6 months from canakinumab start was the dependent variable.

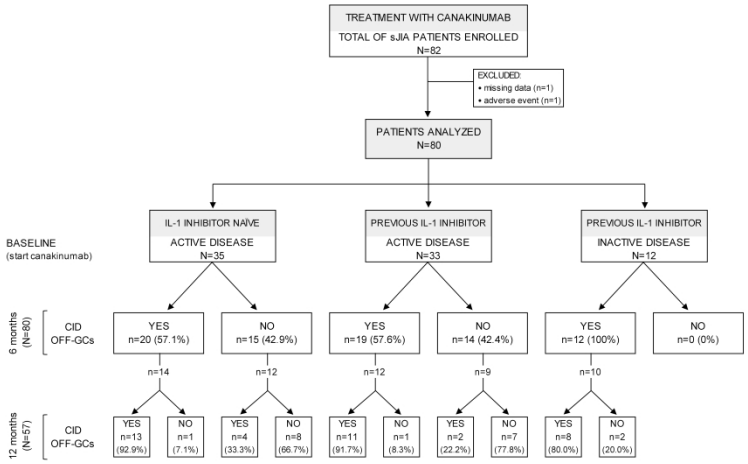

Figure 1 Patient disposition and achievement of clinical inactive disease (CID) off GCs

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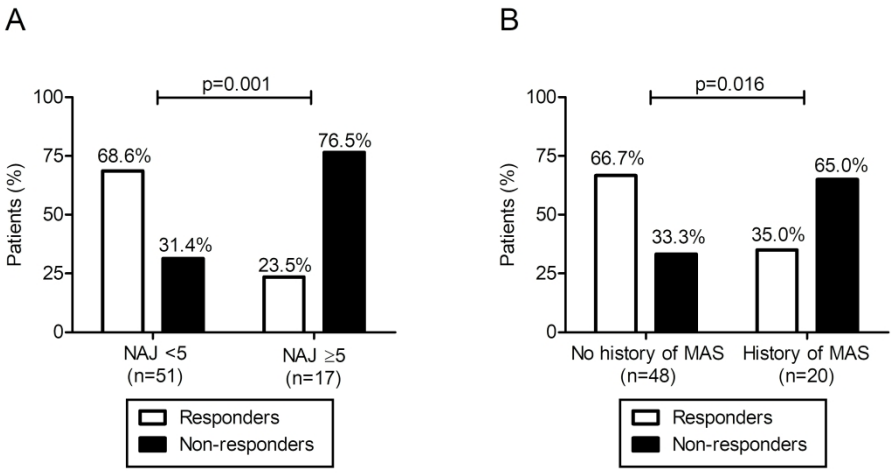

Figure 2. Response after 6 months of therapy with canakinumab. Relationship with the number of active joints (NAJ) at baseline (A) and history of MAS (B). A) Patients with NAJ <5 at baseline had a significantly better response (68.6% vs 23.5%; chi-square test: p=0.001). Risk ratio of non-response at 6 months of therapy with canakinumab based on NAJ ≥5 was 2.4 (95%CI 1.5-4.0). B) Patients without a history of MAS had a significantly better response (66.7% vs 35.0%; chi-square test: p=0.016). Risk ratio of non-response at 6 months of therapy with canakinumab based on history of MAS was 2.0 (95%CI 1.2-3.3).

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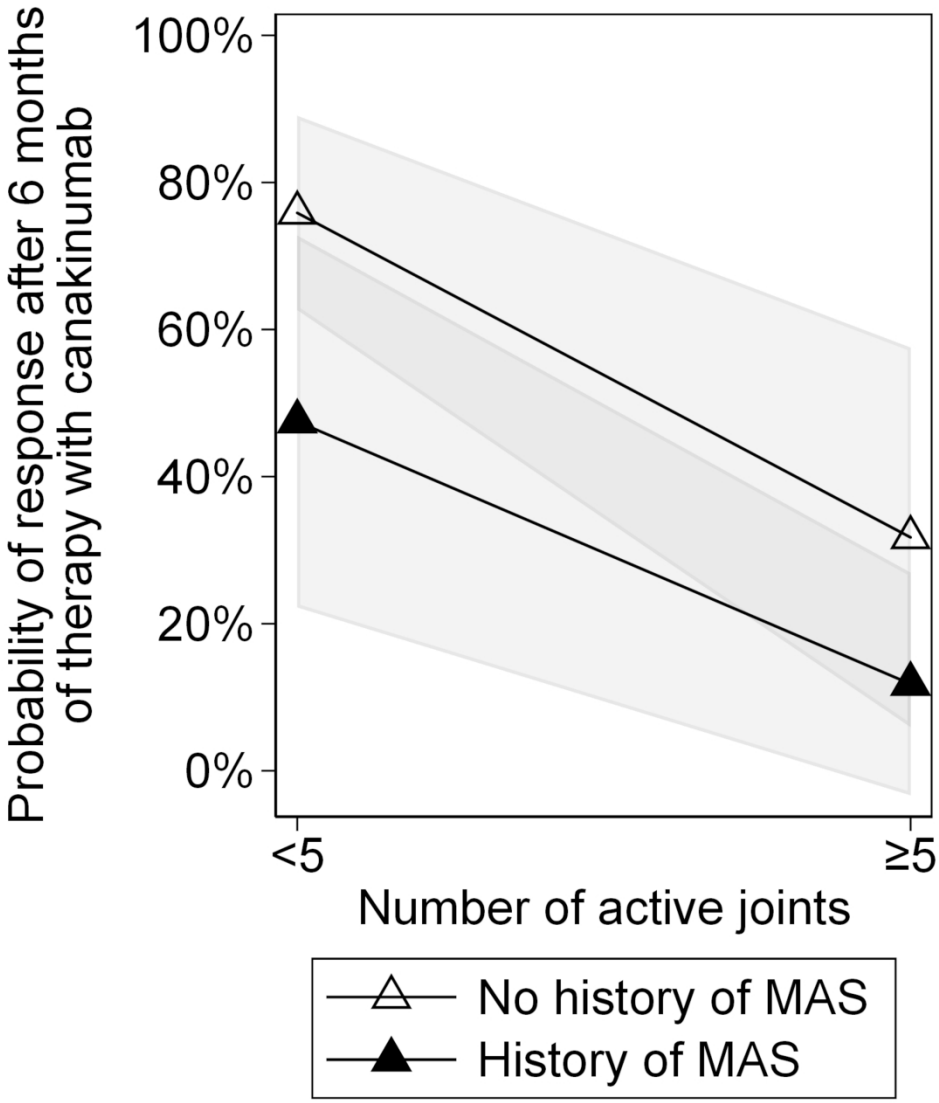

Figure 3. Logistic regression analysis of non-achievement of clinical inactive disease at 6 months from starting canakinumab.
Best-fitting model obtained through logistic regression procedures (Pseudo R2: 0.18). Non-achievement of clinical inactive disease at 6 months from canakinumab start was the dependent variable.

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