Original article

Use of the Auto-inflammatory Disease Activity Index to monitor disease activity in patients with colchicine-resistant Familial Mediterranean Fever, Mevalonate Kinase Deficiency, and TRAPS treated with canakinumab

suppl.
Informations

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ABSTRACT

Objectives: To evaluate the feasibility of the autoinflammatory disease activity index (AIDAI) as a tool to assess disease activity in patients with hereditary recurrent fever syndromes (HRFs) treated with canakinumab.

Methods: Patients with active colchicine-resistant familial Mediterranean fever (crFMF), mevalonate kinase deficiency (MKD), or tumor necrosis factor receptor-associated periodic syndrome (TRAPS) were enrolled in the phase III CLUSTER study and asked to complete the AIDAI questionnaire daily. All patients included in the analysis were treated with canakinumab, but regimens and periods of treatment varied per study protocol. The AIDAI for each patient was calculated weekly over the first 40 weeks of study, based on the diaries completed over 30 days. Disease-specific cut-off AIDAI values for inactive disease were calculated in a ROC analysis by comparing AIDAI scores with the occurrence of clinically inactive disease, based on the physician global assessments of disease activity and the occurrence of flares.

Results: Sixty patients with crFMF, 70 with MKD, and 43 with TRAPS were included in the analysis. Median AIDAI scores were high during the first 4 weeks for the three disease cohorts, and decreased afterwards, with some differences between disease cohorts. AIDAI values of 12.0, 9.6 and 15.5 were obtained as the most optimal thresholds to discriminate patients with inactive disease, with sensitivity and specificity values mostly over 75%.

Conclusions: The AIDAI allows to discriminate between patients with active and inactive HRFs, and can be used in clinical practice to monitor the disease course of patients and the effect of medications.

1. Introduction

Hereditary recurrent fever syndromes (HRF) are rare auto-inflammatory conditions characterized by recurrent attacks of fever accompanied with systemic inflammation. Four interleukin-1

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(IL-1)-mediated monogenic diseases are considered historical prototypes: Familial Mediterranean fever (FMF), mevalonate kinase deficiency (MKD), tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), and cryopyrin-associated periodic syndromes (CAPS) [1,2]. Patients with HRF present with high blood levels of acute phase reactants during the inflammatory flares, including C-reactive protein (CRP) and serum amyloid A (SAA). Even if they share some common features, HRF are genetically different diseases and also show some differences in their clinical manifestations. Patients with FMF have relatively short fever attacks which typically last 1–3 days with polyseritis manifesting as severe abdominal pain, chest pain, myalgia and occasionally arthritis, and erysipelas-like erythema [1,3]. Patients with MKD experience longer fever episodes that usually last 3 to 6 days (up to 14 days), and are often accompanied with headache, abdominal pain, diarrhea and vomiting, arthralgia, myalgia and maculopapular rash [1,4,5]. Patients with TRAPS experience flares that last typically 7-21 days with abdominal pain, severe myalgia, frequent rash, and subcutaneous periorbital oedema [1,6,7].

HRF affect multiple organ systems with potentially severe complications. Increased and deregulated production of IL-1β is a major consequence of the genetic defects that cause these diseases, and explains most of, if not all, the inflammatory manifestations in patients. Treatments are intended to counter inflammation, minimize the number and intensity of flares, and control disease activity between flares, in order to prevent long-term organ damage and improve patient's quality of life [8]. Canakinumab, an IL-1 neutralizing antibody, has been shown to be efficacious in all the four prototypic HRF in clinical trials, and has become standard of care [8–13].

Given the lifelong duration of HRF and the impact on patient's general health and quality of life, monitoring disease activity is essential for evaluating the effectiveness of this therapeutic strategy [14,15]. In addition to physician's clinical assessments of disease activity, assessment tools for obtaining patient-reported outcomes play an important complementary role to allow optimal monitoring of disease activity, overall patient well-being, and response to therapy in patients with HRF.

The autoinflammatory disease activity index (AIDAI) was developed as a scoring system based on patient-reported outcomes for the measurement of disease activity across a wide spectrum of auto-inflammatory diseases including CAPS, FMF, MKD and TRAPS [9,15,16].

Here we report the use of the AIDAI to record disease activity during 40 weeks in patients with crFMF, MKD, and TRAPS who were treated with canakinumab in the phase 3 CLUSTER study [9]. The AIDAI scores were compared with the physician's global assessment of disease activity (PGA) and the measurement of inflammation using C-reactive protein (CRP). We also performed ROC analyses to calculate disease specific AIDAI cut-off scores to discriminate between patients with active and non-active disease, for each of the diseases included in CLUSTER.

2. Methods

2.1. Study design

The design of the CLUSTER study (NCT02059291) has been previously reported in detail [17]. Briefly, efficacy and safety of canakinumab were studied separately on three disease cohorts (crFMF, MKD, and TRAPS) during four study epochs: a screening epoch of up to 12 weeks to assess patients' eligibility (Epoch 1); a randomized treatment epoch of 16 weeks that provided efficacy and safety data in a double-blind, placebo-controlled, parallel-arm setting (Epoch 2); a randomized withdrawal epoch of 24 weeks (Epoch 3); and an open-label treatment epoch of 72 weeks (Epoch 4). Since AIDAI at a given date is calculated on the basis of diaries completed during the previous 30 days, patients started to fill in AIDAI grids during the screening period (Epoch 1), and therefore AIDAI scores were already available at baseline. Recording then continued during epochs 2 and 3, but diaries were not completed during Epoch 4. Therefore, in this article we report results obtained during Epochs 2 and 3 (weeks 1 to 40 of the trial).

Inclusion and exclusion criteria have been previously reported [9]. Patients were eligible to enter the trial (start of Epoch 2) when they experienced a flare of disease (baseline flare), defined as PGA > 2 and CRP > 30 mg/L. In Epoch 2, those patients were randomly assigned to receive subcutaneous (SC) canakinumab 150 mg or placebo every 4 weeks (q4w). The primary objective of the study was to demonstrate that canakinumab treatment at a dose of 150 mg q4w was superior to placebo in achieving a clinically meaningful reduction of disease activity, defined as complete response. Complete response was a composite outcome including resolution of flare by day 15 (physician's global assessment (PGA) <2, and C-reactive protein (CRP) ≤10 mg/L or reduction ≥70% from baseline), and no new flare until week 16 (end of Epoch 2). This primary endpoint was met for the three cohorts of patients, and results have been previously reported [9].

Those patients with no flare resolution by day 15, or who experienced a new flare of disease after that time, received add-on injections of canakinumab 150 mg q4w. There were a few patients who were randomized to placebo and experienced resolution of baseline flare within 15 days and did not experience any flare until the end of Epoch 2 (week 16); those patients were excluded from the analyses reported in this article, which included only patients that required canakinumab treatment for control of disease activity.

At start of Epoch 3, all patients received treatment every 8 weeks (q8w). Patients with a complete response in Epoch 2 underwent a second randomization to receive canakinumab or placebo every 8 weeks (q8w). Non-responders in Epoch 2 received open-label canakinumab 150 or 300 mg q8w. In all cases, doses could be increased and the interval between doses decreased as needed, up to 300 mg q4w [9].

2.2. Assessments

All patients were asked to complete prospectively the AIDAI questionnaire daily during Epoch 1 to 3. This questionnaire, which is patented in Europe for non-institutional use, has 12 items corresponding to disease symptoms (fever ≥38 °C, overall symptoms of a flare, abdominal pain, nausea/vomiting, diarrhea, headaches, chest pain, painful nodes, arthralgia or myalgia, swelling of the joints, eye manifestations, and skin rash), and a value of 0 (absent) or 1 (present) was given to each item by the patient. The AIDAI is calculated as the sum of these values during the last 30 days [15].

The protocol of the CLUSTER study requested the patients or care givers to complete the diary with the AIDAI grid daily, however not all patients complied. To avoid arbitrary imputation, all the scores available from the last 30 consecutive days were added, and the result was corrected by multiplying it for 360 (the total number of scores that can be produced in 30 days) and dividing it by the actual number of scores provided by the patient. Thus, for a patient who answered a total of X items during 30 days, and for whom the sum of scores was Y, this sum was corrected and the final score calculated as $Z = Y \times (360/X)$.

The physician global assessment (PGA) of disease activity was performed at baseline and at each visit every 4 weeks, taking into account fever and abdominal pain in all patients, and the following symptoms associated to each disease: chest pain, arthralgia/arthritis and skin rash for crFMF; lymphadenopathy and

Table 1
Definition of patients with inactive and minimally active disease at a given day "D" used in this analysis.

	Clinically Inactive Disease	Clinically inactive or minimally Active disease	Inactive Disease based on CRP
Physician's Global Assessment of disease activity (PGA)	PGA = 0 both at day D and day D-28 (previous assessment)	PGA = 0 or 1 both at day D and day D-28 (previous assessment)	–
C-reactive protein (CRP)	–	–	CRP < 10 mg/L both at day D and day D-28 (previous assessment)
Occurrence of flares (PGA ≥ 2 and CRP > 30 mg/L)	No flares reported from day D-30 to D	No flares reported from day D-30 to D	No flares reported from day D-30 to D

Table 2
Demographic and baseline characteristics.

Characteristics	crFMF N = 60	MKD N = 70	TRAPS N = 43
Female, n (%)	29 (48.3)	40 (57.1)	20 (46.5)
Caucasian, n (%)	49 (81.7)	62 (88.6)	35 (81.4)
Age, median (Q1–Q3)	18.0 (14–29.5)	11.0 (5.0–17.0)	16.0 (8.0–39.0)
Age category, n (%)			
< 12 years	11 (18.3)	37 (52.9)	16 (37.2)
12–18 years	15 (25.0)	16 (22.9)	9 (20.9)
> 18 years	34 (56.7)	17 (24.3)	18 (41.9)
Age at onset of disease (years); median (Q1–Q3)	3.14 (1.59–7.74)	0.52 (0.25–1.37)	4.72 (1.51–10.67)
Time since first symptoms (years); median (Q1–Q3)	14.56 (9.78–24.20)	9.76 (5.23–16.19)	7.96 (4.53–13.12)
Number of flares per year, median (Q1–Q3)	17.5 (12.0–27.5)	12.0 (10.0–24.0)	9.0 (6.0–12.0)
Duration of flare (days); median (Q1–Q3)	3.0 (2.0–4.50)	4.5 (3.0–6.0)	7.0 (4.0–14.0)
PGA			
Mild	10 (16.7)	16 (22.9)	17 (39.5)
Moderate	33 (55.0)	43 (61.4)	22 (51.2)
Severe	17 (28.3)	11 (15.7)	4 (9.3)
CRP (mg/L), median (Q1–Q3)	110 (58.6–203)	113 (61.0–241)	124 (45.0–216)

N: total number of patients; n: number of patients; PGA: Physician Global Assessment of Disease Activity; CRP: C-reactive protein; Q1: first quartile; Q3: third quartile.

Table 3
Results from ROC analysis.

	crFMF n = 60, m = 319	MKD n = 70, m = 490	TRAPS n = 43, m = 277
AIDAI cut-off value for inactive disease (95%CI)	12.0 (12.0,12.1)	9.6 (9.6, 9.7)	15.5 (15.1, 17.1)
Sensitivity (95% CI), %	75.2 (74.7, 75.7)	65.9 (65.3, 66.4)	81.7 (81.1, 82.3)
Specificity (95% CI), %	79.8 (79.4, 80.1)	76.9 (76.5, 77.5)	84.4 (84.1, 84.8)
AUC (95% CI), %	80.3 (80.0, 80.6)	75.3 (75.0, 75.4)	89.5 (89.2, 89.7)

n: total number of patients included in the analysis; m: number of data points included in the analysis; ROC analysis: receiver operating characteristic analysis; CI: confidence interval; AUC: area under the curve.

aphthous ulcers for MKD; skin rash, musculoskeletal pain and eye manifestations for TRAPS. A 5-point scale was used, with 0, 1, 2, 3 and 4 corresponding to no, minimal, mild, moderate and severe disease activity, respectively [9]. Serum levels of CRP were also determined at each visit, and the occurrence of flares (defined as PGA ≥ 2 and CRP > 30 mg/L) was permanently monitored.

For comparison with the data obtained from the AIDAI, we defined patients with clinically inactive disease (CID), patients with no or minimal clinically active disease, and patients with inactive disease based on CRP assessments (CRP-ID), based on the assessments during the preceding 30-day period, as shown in Table 1.

2.3. ROC analysis

We performed a receiver operating characteristic (ROC) analysis to determine the best cut-off values for discriminating between patients with active and inactive disease for each disease cohort [18]. For each time point included in the analysis, we used the AIDAI scores and the occurrence of CID, both calculated based on assessments from the previous 30 days, as described before. Those assessments were available at 4-week intervals from week 4 to week 40 (according to the described method to calculate CID, the first value available was at week 4, based on PGAs obtained at

baseline and week 4). Thus, we had up to 11 time points available for each patient. Since the number of time points that could be evaluated varied from patient to patient, we applied a bootstrap approach to correct the ROC analysis for multiple measures. The bootstrap analysis was performed through 1000 iterations. In each iteration, all observations from N patients were randomly selected with replacement from the original sample to create a bootstrap replicate. A cut-off value was estimated for each replicate. The final cut-off values were calculated as the median values of the 1000 estimates obtained by the successive iterations. 95% confidence intervals were also calculated to assess the accuracy of the bootstrap approach. The cut-off values were selected as the values with the most hits based on the Youden Criteria, the Distance to the Corner, the Concordance Probability and the Index of Union [19,20]. In case of ties, values resulting from the Concordance Probability criteria were selected. Further details are provided in Data S1 [See the supplementary material associated with this article online].

3. Results

Out of 185 patients enrolled in the CLUSTER study, 12 were excluded from this analysis, as they were never treated with canakinumab and discontinued the study by the end of Epoch 2.

Three of these patients (1 in each cohort) were randomized to placebo and discontinued the study during Epoch 2. Nine more patients (N= 4, 3, and 2 for the crFMF, MKD, and TRAPS cohorts, respectively) were on placebo throughout Epoch 2, had resolution of their baseline flare within 29 days with no new disease flares afterwards, and ended the study at the end of Epoch 2 as per protocol. Sixty patients with crFMF, 70 with MKD, and 43 with TRAPS were included in the analysis, of whom 2, 5 and 5 discontinued the study before the end of Epoch 3 (a detailed patient disposition chart for the CLUSTER study has been previously reported) [15]. Demographics and baseline characteristics are presented in Table 2. Most patients were Caucasian, and there were slightly more females in the MKD cohort (57%). It should be noted that the patient populations involved in this study reported relatively high levels of disease activity during the previous year, with a median rate of flares per year of 17.5, 12.0 and 9.0 for patients with crFMF, MKD, and TRAPS, respectively. Taking into account the rate of flares and their average duration reported by each patient, we estimated that the median number of days per year that patients were having a disease flare prior to the study was 60, 60 and 70 for patients with crFMF, HIDS and TRAPS, respectively.

3.1. Evolution of AIDAI scores overtime

Fig. 1 shows the evolution of the AIDAI from baseline to week 40, for each cohort of patients. AIDAI was calculated at baseline (day 1)

and every 7 days afterwards, based on the diary completed during the last 30 days before that date (included). For some patients, data was missing for some of the days, and therefore we calculated scores considering, for each particular time-point (i) all patients (6725 patient-time points available in total), and patients who completed the diary for (ii) at least 15 days (6237 patient-time points, 93% of all points available), and (iii) for at least 23 days (5281 patient-time points, 79% of all points available). Overall, a similar evolution over time could be observed for these three sets of patients, in each of the three cohorts analyzed. We considered that data-points based on AIDAI from diaries that were filled in at least 50% of the days (i.e., at least 15 days) represented well the population and allowed to discard few data-points with many missing items.

Therefore, we selected this option for subsequent analyses.

As expected, AIDAI scores were high during the first 4 weeks for the three cohorts, since a flare at baseline was required for patients to enter the study, but scores were clearly higher for patients with TRAPS (median values ranging from 70 to 84) than for the other two cohorts (median values ranging from 38 to 51). Median AIDAI scores remained relatively low from week 4 through week 16, although they were slightly but consistently different between cohorts, with higher values for patients with TRAPS and lower values for patients with crFMF. After week 20, values remained constantly low in patients with MKD, whereas a remarkable increase was observed from week 22 to week 32 in patients with TRAPS, and a small increase was noted from week 30 to week 36 in patients with crFMF.
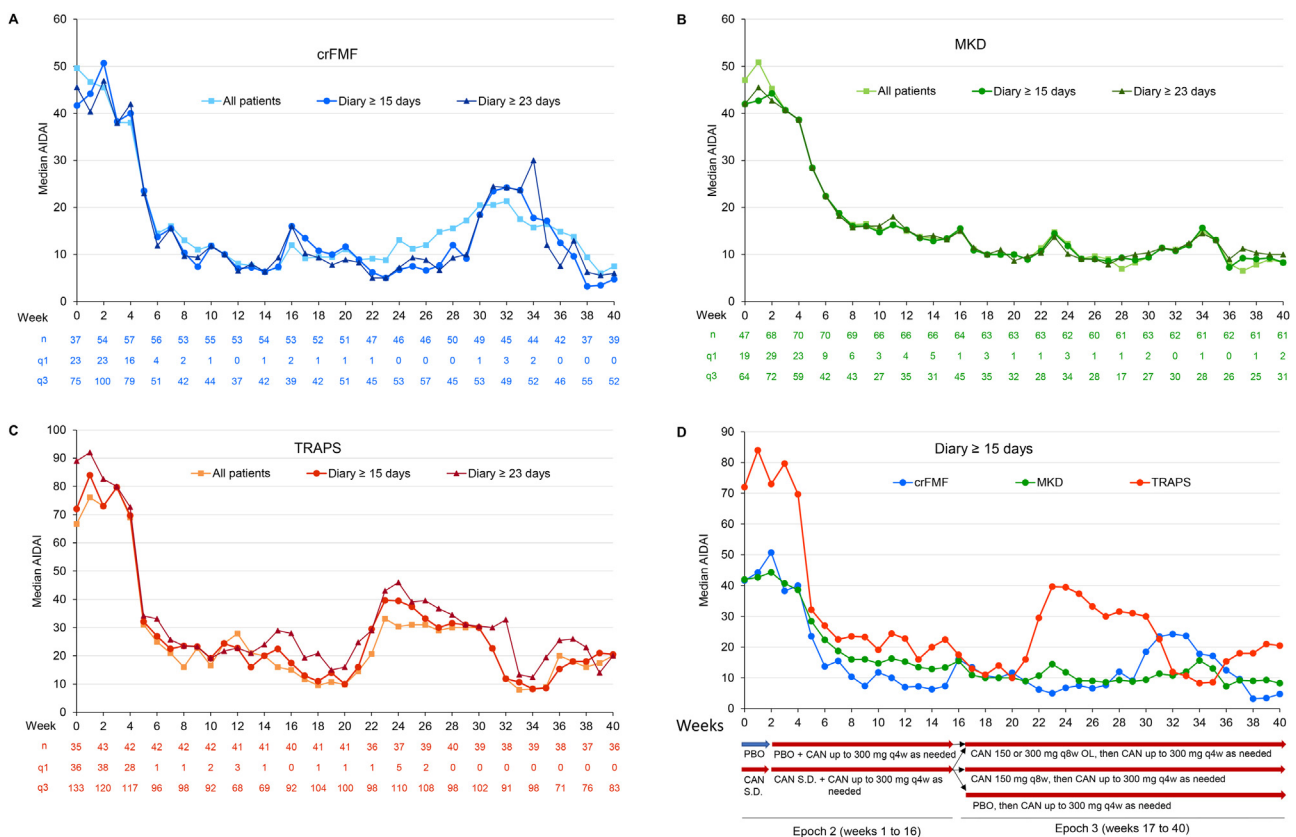

Fig. 1. AIDAI scores over 40 weeks. Plots A–C show the median AIDAI scores calculated once per week during 40 weeks for patients with crFMF (A), HIDS/MKD (B) and TRAPS (C). For each time-point, medians were calculated using either all patients with at least one score available, or patients that fulfilled at least 15 or 23 days out of the 30 days of the diary. Under each plot, the total number of patients (*n*), the first quartile (q1) and third quartile (q3) are presented every two weeks for patients that fulfilled at least 15 days of diary. Fig. D presents the data of the three cohorts from patient who fulfilled at least 15 days of diary, whereas the sequence of treatment during the 40 weeks is detailed below. "As needed" indicated that dosing of canakinumab was started or increased, or dose interval shortened, according to the occurrence of flares and as per physician's judgement, up to a maximum dose of 300 mg q4w. PBO, Placebo; CAN, canakinumab; S.D., standard dose of 150 mg every 4 weeks; q4w, every 4 weeks; q8w, every 8 weeks.
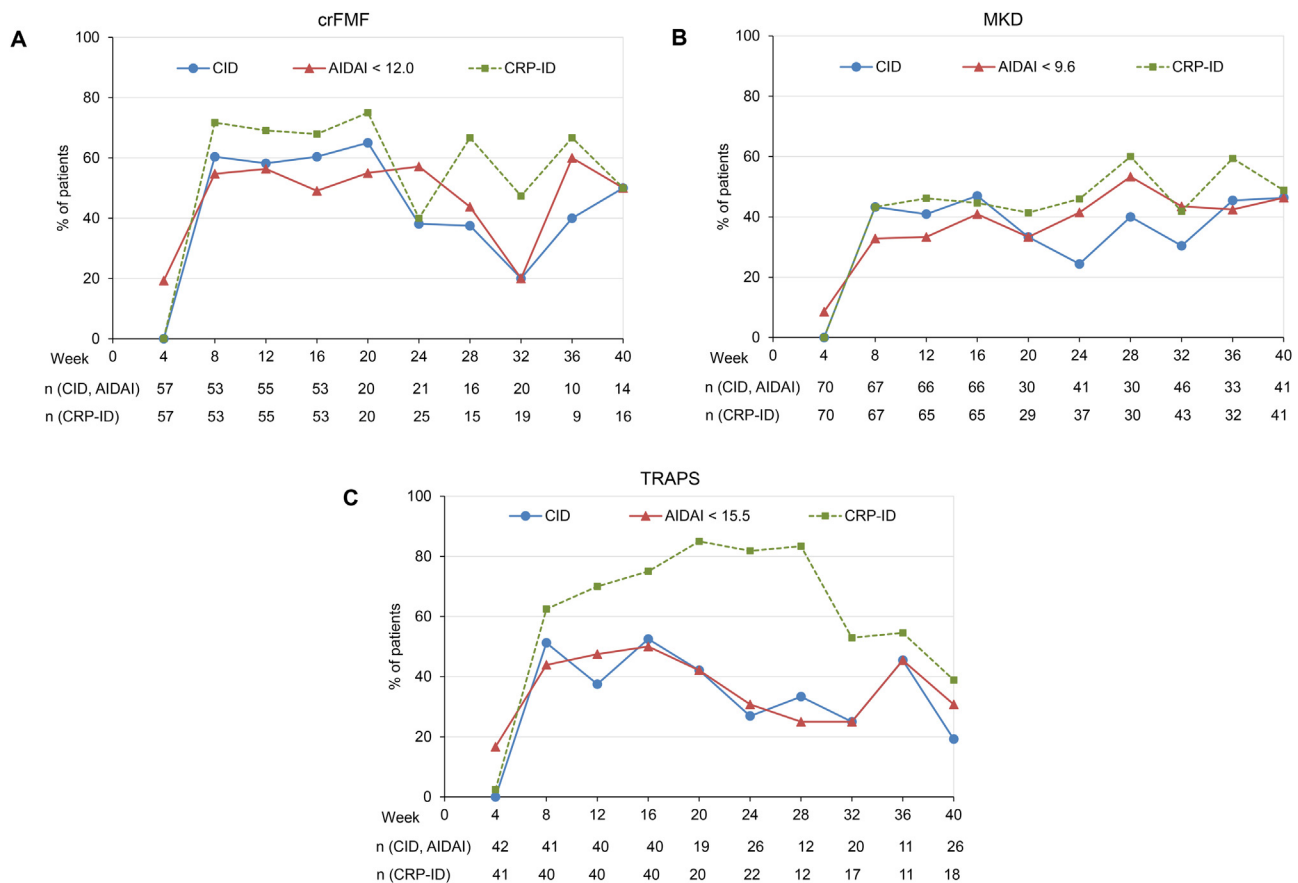
Fig. 2. Proportion of patients with inactive disease according to clinical, biological, and AIDAI assessments. Graphics present the percentage of patients with clinically inactive disease (CID), inactive disease based on CRP assessments (CRP-ID) and AIDAI scores under the cut-off value calculated through ROC analysis in patients with crFMF (A), MKD (B) and TRAPS (C) from week 4 to week 40. CID is defined as PGA = 0 at the given time point and at the previous assessment 28 days before, plus absence of flares (defined as PGA > 1 and CRP > 30 mg/L) in the last 30 days. CRP-ID is defined as CRP < 10 mg/L at the given time-point and at the previous assessment 28 days before, plus no flares reported in the last 30 days. AIDAI scores are calculated based on diaries fulfilled during the last 30 days. Below each graphic, n represents the number of patients included in each time point. PGA, physician global assessment of disease activity; CRP, C-reactive protein.

3.2. Disease-specific cut-off AIDAI values for discriminating patients with active/inactive disease

We performed a ROC analysis to calculate the AIDAI cut-off scores that better allowed to discriminate patients with CID, defined as PGA = 0 in the last two measurements and absence of flares in the last 30 days, from those with disease activity. As shown in Table 3, AIDAI values of 12.0, 9.6 and 15.5 were obtained for the crFMF, MKD and TRAPS cohorts. Sensitivity and specificity values were mostly over 75%. ROC analyses were also performed for calculating values that better discriminated patients with inactive or minimally active disease (PGA = 0 or 1 in the two measurements, and no flares reported). However, obtained values of specificity and sensitivity were below the 70% threshold for all the three cohorts, and further analyses indicated that the calculated cut-off values did not allow a good discrimination of patients with minimal or no disease activity for some time-points (data not shown).

3.3. Evolution over time of the proportion of patients with inactive disease as assessed by clinical assessment, serological assessments and the AIDAI

Fig. 2 shows the evolution from week 4 to week 40 of the proportion of patients presenting with CID, with CRP-ID (defined as CRP < 10 mg/L in the last two assessments plus the absence of flares in the last 30 days) or with AIDAI scores lower than the threshold value calculated using ROC analysis. As expected, no patients at

week 4 presented with CID or CRP-ID disease due to the baseline flare. After that, the proportion of patients with CID increased at week 8, and remained relatively stable until week 16–20, where it decreased again. As expected, the proportion of patients with AIDAI scores lower than the defined cut-off values followed a similar evolution to that shown with CID. The evolution of patients without serological signs of disease activity as measured by CRP evolved in a similar way for patients with crFMF and MKD, whereas it was clearly different in patients with TRAPS, with a much higher proportion of patients with CRP levels under 10 mg/L from week 12 to week 32. In addition, we compared the evolution of the proportion of patients with CID and AIDAI lower than the cut-off values for patients younger and older than 18 years (Fig. 3), and we found similar results in both populations.

4. Discussion

The use of patient-reported assessment tools must be integrated together with clinical and serological assessments in order to obtain a full picture of the disease activity experienced by the patient. Monitoring disease activity in patients with HRF is very important, in order to optimize their management and minimize long-term complications, including organ damage. In addition, it may contribute to increased adherence to treatment. The AIDAI was developed as a patient/caregiver reported outcome that allows to monitor disease activity without the direct intervention of the physician. Moreover, AIDAI provides information on how patients
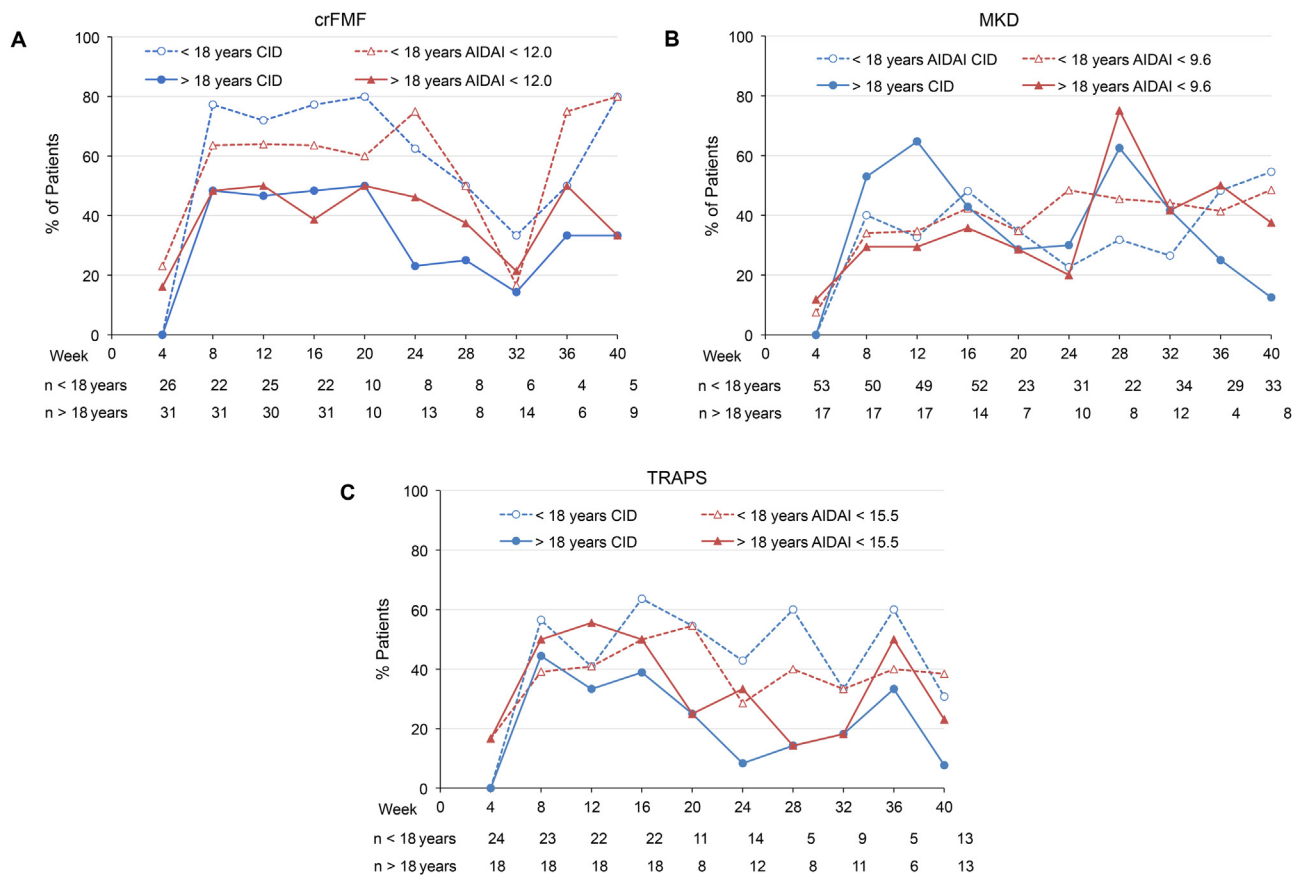
Fig. 3. Proportion of patients younger and older than 18 years with inactive disease according to clinical assessment and AIDAI. Graphics present percentages of patients with clinically inactive disease (CID) and AIDAI scores under the cut-off value calculated through ROC analysis in patients with crFMF (A), MKD (B) and TRAPS (C) from week 4 to week 40. CID is defined as PGA = 0 at the given time point and at the previous assessment 28 days before, plus absence of flares (defined as PGA > 1 and CRP > 30 mg/L) in the last 30 days. Below each graphic, n represents the number of patients included in each time point. PGA, physician global assessment of disease activity; CRP, C-reactive protein.

(or parents/guardians) perceive the activity of the disease in real time, which is complementary to biological and clinical assessments of disease activity which are only evaluated at specific points.

In this study, we used AIDAI to monitor patients with three HRF during 40 weeks in a clinical setting. Median AIDAI scores during the first four weeks were high in the three cohorts due to the baseline flare, the observation that scores were much higher in patients with TRAPS is consistent with the longer duration of flares in this disease. The increase in median AIDAI scores observed in patients with TRAPS and crFMF after week 16 may be related to the change of dosing at this point, where some patients were randomized to placebo and the others had an increase in the dosing interval from q4w to q8w. Interestingly, median AIDAI scores remained low and stable in patients with MKD. It should be noted that all patients received treatment with canakinumab as needed from week 2 to week 40, up to a dose of 300 mg q4w, and therefore no differences between patients initially treated for 2 weeks with placebo or canakinumab were expected to be apparent in the AIDAI, as the tool includes a 30-day observation period.

A validation of the AIDAI was performed in 2010, using pooled data from 98 patients with HRF (FMF, CAPS, HIDS or TRAPS). Patients completed the AIDAI questionnaire for 31 days, and after that they had a clinical appointment during which their physicians assessed their disease activity using a questionnaire. Eight international experts in auto-inflammatory diseases evaluated the patient's disease activity by a blinded web evaluation based on the questionnaire, and an AIDAI value of 9 was calculated to be the best cut-off score to discriminate active from inactive patients,

using a ROC analysis. This study was based on a single assessment for each patient, and data from the four diseases was pooled for the analysis [17].

The relatively large set of data from the CLUSTER study provided a unique opportunity to use the AIDAI for the first time in a clinical trial setting, and to compare it with clinical assessments of disease activity and obtain disease-specific cut-off values to discriminate between patients with active or inactive disease. The values obtained in this study were higher than the previously recommended threshold of 9, and not surprisingly, they varied considerably between diseases. It should be noted that the sensitivity and specificity values obtained are not as high as those reported in the previous validation of AIDAI. We think this is not surprising, considering the differences in the methodology used. In addition, the patient population included in the CLUSTER trial was selected for having relatively high disease activity, while this was not the case for the AIDAI validation study.

We tried to determine thresholds for discriminating patients with no disease activity vs patients with minimal disease activity, but the values obtained for specificity and sensitivity were consistently below the 70% threshold. Moreover, for some time-points, the number of patients presenting minimal, or no disease activity was clearly different from those under the calculated AIDAI cut-off value. Therefore, we conclude that the AIDAI may not be appropriate to discriminate between patients with no or minimal disease activity.

Proportions of patients with CID and AIDAI values below the calculated cut-off values evolved similarly over time. A similar pattern

over time was also obtained when inactive disease was based on the analysis of CRP, except for patients with TRAPS. In this cohort, CRP values below 10 mg/L were frequent even in patients with PGA indicating inactive disease and AIDAI scores under the cut-off values, further reflecting the differences between these diseases. Proportions of patients with CID and AIDAI values below the calculated cut-off values seemed to be similar both in adults and pediatric patients, and the fact that scores were filled in by parents or guardians for the latter did not seem to influence the results. Therefore, measuring disease activity does not appear to be influenced by age, differently from what happens with tools for measuring quality of life that are typically different for children and adults.

In any case, we believe that patient/caregiver-reported assessment tools provide information complementary to the clinical and biological assessments of disease activity, and therefore is important to note that a very strong correlation is not necessarily expected between these parameters.

Limitations of this study include the lack of a control group of patients receiving placebo only, due to the study design, and the relatively low number of patients with measurements available after week 16 for performing comparisons between CID and AIDAI. The AIDAI score contains subjective items and we cannot completely exclude that the pediatric patient's caregivers may have misinterpreted theirs values.

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Disclosure of interest

IK-P has received grants from SOBI and LFB, and has been a consultant for Novartis, Sobi, Pfizer, Chugai, Abbvie and LFB. IK-P and MP are shareholders of Patent Valor, exclusive licensee for the AIDAI score. JK-D has received grants from Novartis and SOBI and has been a consultant for Novartis and SOBI. SB, AJ, IR, AT, SM and OK declare that they have no competing interests. JL is a consultant for Novartis. SMC is an employee of Novartis. MM is a consultant for Novartis. FDB has received grants from Novimmune, Novartis, SOBI, Abbvie, Roche and Sanofi.

Contributors Statement

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, were involved in the drafting and critical review of the manuscript and approved the final version for submission. All authors agree to be accountable for all aspects of the work and attest to the accuracy and integrity of the work.

Ethics approval and consent to participate

All study protocols and its amendments were reviewed and approved by the independent ethics committee or institutional review board for each participating center. The study was conducted according to the International Council for Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP) that has its origin in the Declaration of Helsinki. Written informed consent was obtained from all enrolled patients. Data were collected in accordance with the GCP guidelines by the study investigators and analyzed by the sponsor.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available. Novartis is committed to sharing with qualified external researchers' access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved based on scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The data may be requested from the corresponding author of the manuscript.

Significance and Innovation

AIDAI is a tool for the assessment of disease activity as reported by patients or parents/guardians across a wide spectrum of auto-inflammatory diseases, it provides information complementary to the physician's clinical assessment and measurements of biomarkers.

This study uses AIDAI to assess evolution of disease activity in patients with crFMF, MKD, or TRAPS treated with canakinumab in a phase III study. The results are compared with clinical and serological assessments of disease activity, and disease-specific cut-off AIDAI values for inactive disease are calculated using a ROC analysis, together with sensitivity and specificity parameter.

This study provides an empirical basis and appropriate cut-off values for using AIDAI to assess disease activity and well-being of patients with crFMF, MKD, and TRAPS. The AIDAI can be used in clinical practice to monitor the evolution of patients and the effect of medications.

Acknowledgments

Appendix A. Supplementary data

Supplementary data (Data S1) associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2022.105448.

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