External Validation of the Auto-inflammatory Disease Activity Index (AIDAI) in Patients with Colchicine-Resistant FMF, HIDS/MKD, and TRAPS: Results from a Pivotal, Phase 3 Trial of Canakinumab

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Introduction

- Recurrent fever syndromes are a group of rare auto-inflammatory conditions that include cryopyrin-associated periodic syndromes (CAPS), familial Mediterranean fever (FMF), hyper-immunoglobulin (Ig) D syndrome/mevalonate kinase deficiency (HIDS/MKD), and tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) (1, 2)
- Increased production of interleukin (IL)-1β has been shown to be involved in the pathophysiology of FMF, HIDS/MKD, and TRAPS (3–5)
- To date, there is no standardized assessment tool to distinguish between different levels of disease activity and response to therapy in FMF, HIDS/MKD, and TRAPS. The lack of such standardized measures for assessing disease activity hampers the implementation of targeted therapies and comparison of treatment outcomes in these recurrent fever syndromes (6, 7)
- Autoinflammatory Disease Activity Index (AIDAI) is a novel, validated patient-reported assessment tool for the measurement of disease activity across a wide spectrum of auto-inflammatory diseases including CAPS, FMF, HIDS/MKD, and TRAPS (6, 7)
- AIDAI scoring system has not yet been validated in clinical studies to distinguish between different levels of disease activity in FMF, HIDS/MKD, and TRAPS
- Here we present the data for disease activity using AIDAI scores in patients with colchicine-resistant (cr) FMF, HIDS/MKD, or TRAPS from a phase III, randomized, double-blind, placebo-controlled trial (CLUSTER; NCT02059291) (8)

Objectives

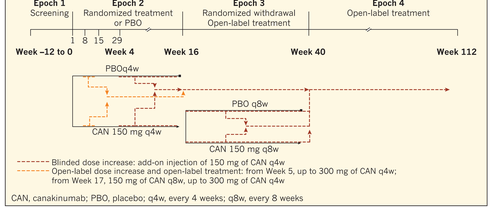
- External validation of AIDAI by calculating scores over 40 weeks of treatment with canakinumab, a human anti-IL-1 monoclonal antibody, in crFMF, HIDS/MKD, or TRAPS patients from the CLUSTER study (8)
- To assess the correlation between AIDAI score and other disease activity variables including Sheehan disability scale (SDS), child health questionnaire–psychological/physical (CHQ–PsCS/PCS), short-form 12 physical/mental component (SF12–PCS/MCS) summaries, physician's global assessment (PGA), C-reactive protein (CRP), and serum amyloid A (SAA) levels

Methods

Study design

- The trial comprised of three disease cohorts (crFMF, HIDS/MKD, and TRAPS) and four study epochs (**Figure 1**) (8)
  - A screening epoch of up to 12 weeks to assess patients' eligibility
  - A randomized treatment epoch of 16 weeks that provided efficacy and safety data in a double-blind, placebo-controlled, parallel-arm setting
  - A randomized withdrawal epoch of 24 weeks
  - An open-label treatment epoch of 72 weeks
- Patients who were initially randomized to canakinumab 150 mg (or 2 mg/kg in patients weighing ≤40 kg) every 4 weeks (q4w) and did not experience a flare in epoch 2 were re-randomized 1:1 to canakinumab 150 mg every 8 weeks (q8w) or placebo in epoch 3 (**Figure 1**)
  - Patients whose disease flare had not resolved before Day 29 were uptitrated blindly to the next dosing regimen. Patients receiving placebo received 150 mg (or 2 mg/kg for patients weighing ≤40 kg) q4w
  - Patients receiving canakinumab were uptitrated to 300 mg (or 4 mg/kg for patients weighing ≤40 kg) q4w

Figure 1. Study design



CAN, canakinumab; PBO, placebo; q4w, every 4 weeks; q8w, every 8 weeks

Assessments

- The AIDAI score was calculated as the sum of 12 items (fever ≥38°C, overall symptoms, abdominal pain, nausea/vomiting, diarrhea, headaches, chest pain, painful nodes, arthralgia or myalgia, swelling of the joints, eye manifestations, and skin rash) for 30 consecutive days (7) from baseline to Week 40
- Inactive disease was indicated by AIDAI score <9
- AIDAI and inactive disease were calculated in:
  - overall population (responders and non-responders) of each cohort
  - primary outcome responders [patients with a resolution of disease flare (PGA <2 and CRP ≤10 mg/L, or reduction ≥70% from baseline) at Day 15 and did not experience a new flare up to Week 16] without titration
  - primary outcome responders including patients who were up-titrated to 300 mg q4w
- The correlation of AIDAI score with SDS, CHQ–PsCS/PCS, SF12–PCS/MCS, PGA, and CRP and SAA levels was assessed at baseline and q4w from baseline

Statistical analysis

- The AIDAI score was calculated if the first score was recorded before ≥29 days
- Missing AIDAI assessments between the first and last assessments were imputed with 'No'
- Missing AIDAI assessments after last assessment were imputed with last observation carried forward (LOCF), if last AIDAI assessment within the visit window
  - Visit window = Day +3 days / -24 days. For patients with >1 assessment within the visit window, only the closest assessment to the scheduled visit date is taken into account
- Correlation for continuous parameters is based on the Pearson correlation coefficient and correlation for ordinal parameters is based on the Spearman's coefficient

Results

- Baseline demographic and clinical characteristics were balanced in epoch 2 and 3 across three cohorts (**Table 1**)

Table 1. Demographic and baseline characteristics

Characteristics	Epoch 2			Epoch 3		
	crFMF (N=63)	HIDS/MKD (N=72)	TRAPS (N=46)	crFMF (N=59)	HIDS/MKD (N=66)	TRAPS (N=42)
Median age, years (min, max)	18 (2, 69)	11 (2, 47)	15.5 (2, 76)	18 (2, 69)	11.5 (2, 47)	16 (2, 76)
Female, n (%)	29 (46.0)	43 (59.7)	23 (50.0)	27 (45.8)	39 (59.1)	20 (47.6)
Caucasian, n (%)	54 (85.7)	65 (90.3)	38 (82.6)	50 (84.7)	59 (89.4)	35 (83.3)
Median no. of flares/ year (min, max)	18 (3, 156)	12 (4, 26)	9 (3, 30)	18 (3, 156)	12 (4, 25)	9 (3, 30)
Median CRP, mg/L (min, max)	94 (10, 503)	113.5 (10, 614)	112.5 (1, 855)	110 (10, 503)	111 (10, 614)	127.1 (1, 855)
Median SAA, mg/L (min, max)	600 (6, 10856)	2725 (6, 12000)	1078.5 (4, 12000)	636 (6, 10856)	1797 (6, 12000)	1155.5 (4, 12000)

N, total number of patients; n, number of patients with response. max, maximum; min, minimum

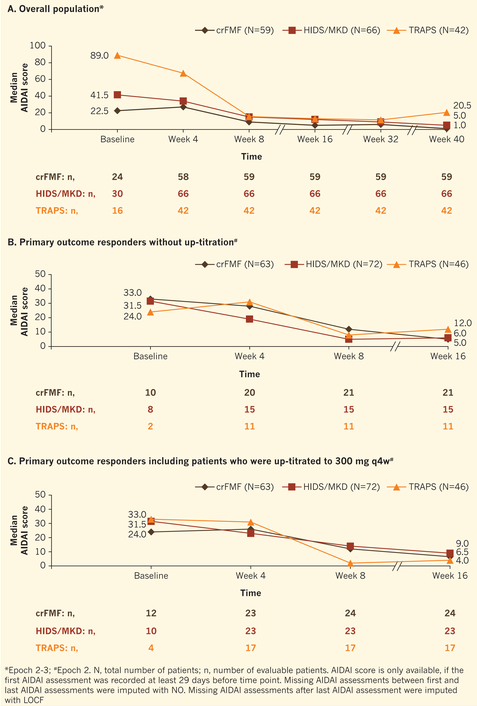
Median AIDAI score

- In the overall population, the median AIDAI score decreased from baseline to Week 16 across all three cohorts (crFMF, 22.5 to 5.0; HIDS/MKD, 41.5 to 12.0; TRAPS, 89.0 to 13.0), and sustained or further decreased through 40 weeks (crFMF, 1.0; HIDS/MKD, 5.0; TRAPS, 20.5; **Figure 2A**)
- At Week 16, the median AIDAI score was lower compared to baseline in the primary outcome responders without up-titration and in the primary outcome responders including patients who were up-titrated to 300 mg q4w. Results were comparable in both the groups (**Figure 2B and C**)

Inactive disease (AIDAI <9)

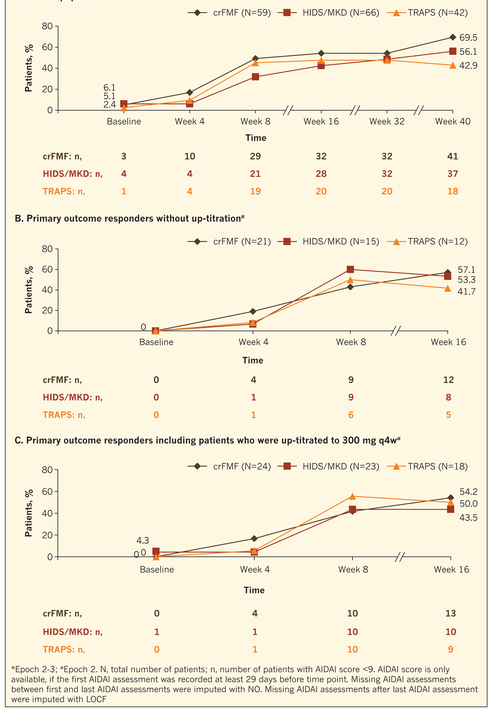
- The proportion of patients with inactive disease within each cohort was greater at Week 16 compared with the start of epoch 2 in the overall population (crFMF, 54.2 vs 5.1; HIDS/MKD, 42.4 vs 6.1; TRAPS, 47.6 vs 2.4), and was sustained or further increased through 40 weeks (crFMF, 69.5; HIDS/MKD, 56.1; TRAPS, 42.9; **Figure 3A**)
- Similarly, the proportion of patients with inactive disease within each cohort was greater at Week 16 compared to the start of epoch 2 in the primary outcome responders without titration and in the primary outcome responders including patients who were up-titrated to 300 mg q4w. Results were comparable in both the groups (**Figure 3B and C**)

Figure 2. Median AIDAI score



*Epoch 2-3; *Epoch 2. N, total number of patients; n, number of evaluable patients. AIDAI score is only available, if the first AIDAI assessment was recorded at least 29 days before time point. Missing AIDAI assessments between first and last AIDAI assessments were imputed with NO. Missing AIDAI assessments after last AIDAI assessment were imputed with LOCF

Figure 3. Proportion of patients with inactive disease



*Epoch 2-3; *Epoch 2. N, total number of patients; n, number of patients with AIDAI score <9. AIDAI score is only available, if the first AIDAI assessment was recorded at least 29 days before time point. Missing AIDAI assessments between first and last AIDAI assessments were imputed with NO. Missing AIDAI assessments after last AIDAI assessment were imputed with LOCF

Correlation of AIDAI score and disease activity variables

- At Week 16, AIDAI scores were significantly correlated with: SDS in the crFMF and TRAPS cohorts, PGA in the TRAPS cohort, and SF12-PCS in the crFMF cohort. At Week 40, AIDAI scores were significantly correlated with: SDS in all three cohorts, CHQ-PsCS in the crFMF and HIDS/MKD, CHQ-PCS in the crFMF, PGA in the TRAPS and SF12–PCS in the crFMF and HIDS/MKD cohorts (**Table 2**)
  - No significant correlation was observed between AIDAI and SF12-MCS, CRP, and SAA at Weeks 16 and 40

Table 2. Correlation between AIDAI and disease activity variables at Weeks 16 and 40#

Variables	crFMF (N=59)		HIDS/MKD (N=66)		TRAPS (N=42)	
	Week 16	Week 40	Week 16	Week 40	Week 16	Week 40
SDS, n	40	28	36	33	27	25
CC (95% CI)	**0.43* (0.13; 0.65)**	**0.54* (0.20; 0.76)**	0.29 (-0.04; 0.56)	**0.39* (0.05; 0.65)**	**0.38* (0.0; 0.66)**	**0.41* (0.02; 0.69)**
CHQ-PsCS, n	17	12	24	20	14	12
CC (95% CI)	−0.15 (−0.59; 0.35)	**−0.83* (−0.95; −0.49)**	−0.26 (−0.60; 0.16)	**−0.47* (−0.76; −0.03)**	−0.45 (−0.79; 0.11)	−0.07 (−0.62; 0.53)
CHQ-PCS, n	17	12	24	20	14	12
CC (95% CI)	−0.25 (−0.65; 0.26)	**−0.67* (−0.90; −0.16)**	**−0.52* (−0.76; −0.15)**	−0.32 (−0.67; 0.14)	−0.44 (−0.79; 0.11)	−0.02 (−0.59; 0.56)
PGA, n	56	40	59	54	40	32
CC (95% CI)	0.24 (−0.02; 0.48)	0.24 (−0.08; 0.51)	0.19 (−0.06 ; 0.43)	0.24 (−0.03; 0.47)	**0.75* (0.57; 0.86)**	**0.37* (0.02; 0.63)**
SF12-PCS, n	25	18	7	9	13	14
CC (95% CI)	**−0.44* (−0.71; −0.05)**	**−0.47* (−0.77; 0.0)**	−0.35 (−0.87; 0.54)	−0.09 (−0.71; 0.61)	−0.49 (−0.82; 0.08)	**−0.60* (−0.86; −0.11)**
SF12-MCS, n	25	18	7	9	13	14
CC (95% CI)	−0.35 (−0.65; 0.05)	−0.43 (−0.75; 0.05)	0.35 (−0.55; 0.87)	−0.19 (−0.76; 0.54)	0.10 (−0.47; 0.62)	−0.13 (−0.62; 0.43)
SAA, n	53	39	52	52	38	30
CC (95% CI)	0.02 (−0.25; 0.29)	−0.07 (−0.38; 0.25)	−0.06 (−0.33; 0.22)	0.06 (−0.22; 0.32)	0.08 (−0.25; 0.39)	−0.17 (−0.50; 0.20)
CRP, n	56	40	59	53	40	31
CC (95% CI)	−0.12 (−0.37; 0.14)	−0.07 (−0.38; 0.24)	0.21 (−0.05; 0.44)	0.08 (−0.19; 0.34)	0.13 (−0.19; 0.42)	−0.18 (−0.51; 0.18)

*Epoch 2-3. *p<0.05. N, total number of patients in the cohort; n, number of evaluable patients
Missing AIDAI assessments between first and last AIDAI assessments were imputed with NO. Missing AIDAI assessments after last AIDAI assessment were imputed with last observation carried forward, if last AIDAI assessment within the visit window. Visit window = Day +3 days / -24 days. For patients with >1 assessment within the visit window, only the closest assessment to the scheduled visit date is taken into account. Correlation for continuous parameters is based on the Pearson correlation coefficient and correlation for ordinal parameters is based on the Spearman's coefficient
CC, correlation coefficient; CI, confidence interval

Conclusions

- Canakinumab demonstrated rapid and sustained disease control over 40 weeks, as assessed using AIDAI scores
- The AIDAI score is a validated patient-reported tool for assessing disease activity in crFMF, TRAPS, and HIDS/MKD, with the potential to be used as the standard efficacy measure in clinical practice for monitoring treatment efficacy and well-being of patients with auto-inflammatory diseases

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