Canakinumab improves patient-reported outcomes in children and adults with autoinflammatory recurrent fever syndromes: results from the CLUSTER trial

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Received on November 23, 2020; accepted in revised form on May 17, 2021.

Clin Exp Rheumatol 2021; 39 (Suppl. 132): S51-S58.

Key words: autoinflammatory diseases, biologicals, cytokines, familial Mediterranean fever, quality of life

Funding: the study was funded by Novartis Pharma AG.
Competing interests: H.J. Lachmann has received consultancy and speaking fees from Novartis and SOBI. B. Lauwerys is currently employed by UCB. T. Kallinich has received consultancies, speaking fees and honoria from Roche, BMS, SOBI, and Novartis. S. Savic has received educational support, consultancy and speaking fees from CSL, Novartis, Takeda, Grifols and SOBI, and received research grants from CSL and SOBI. S. Smeets is an employee of Novartis Pharma AG, Switzerland. F. De Benedetti has received speaking fees and unrestricted research grants from Abbvie, Novartis, Novimmune, SOBI, Pfizer, Roche and Sanofi. The other co-authors have declared no competing interests.

ABSTRACT

Objective. *To evaluate the effect of canakinumab on health-related quality of life (HRQoL), work/school and social life of patients with autoinflammatory recurrent fever syndromes, including colchicine-resistant familial Mediterranean fever, mevalonate kinase deficiency, and tumour necrosis factor receptor-associated periodic syndrome, in the CLUSTER trial.*

Methods. *HRQoL of patients who received canakinumab 150 mg or 300 mg every four weeks in the CLUSTER trial (n=173) was assessed at baseline and Weeks 17 and 41. For children we used the Child Health Questionnaire - Parent Form 50 (CHQ-PF50), including psychosocial (PsS) and physical (PhS) component summary scores. For adults, the Short-Form-12 (SF-12) Health Survey was used, including physical (PFS) and mental (PCS) component summary scores. The Sheehan Disability Scale (SDS) was used to determine the impact of treatment on work/school, social and family life.*

Results. *The results obtained were remarkably consistent in both paediatric and adult patients across the three disease cohorts. At baseline, median scores for physical components were relatively low (26–29 for PhS and 34–38 for PFS); they improved to values similar to those expected in the general population by Week 17, and this improvement was sustained at Week 41, when median PhS scores were 47–50 and PFS 44–54. Psychosocial and mental scores also improved from baseline to Week 17 and 41, with scores comparable to the general population. Notable improvements were also observed in the SDS scale.*

Conclusion. *Patients with three inherited autoinflammatory syndromes experienced sustained improvements on their HRQoL, work/school, and social life on treatment with canakinumab.*

Introduction

Familial Mediterranean fever (FMF), mevalonate kinase deficiency (MKD), and tumour necrosis factor receptor-associated periodic syndrome (TRAPS) are genetic autoinflammatory diseases characterised by recurrent symptomatic flares. Disease flares are characterised by systemic inflammation with constitutional symptoms and variable skin, joint and serosal involvement, resulting in a combination of symptoms which may help differ one syndrome from another (1-5). Attacks are debilitating and can last for several days or weeks. If left untreated these diseases can lead to complications including irreversible organ damage caused by AA amyloidosis, joint damage, growth retardation, and neurological damage with cognitive impairment (6-8). Both acute flares and long-term complications of FMF, MKD, and TRAPS substantially impact patients' health-related quality of life (HRQoL) (9-12).

The systemic autoinflammatory syndromes are rare disorders, with estimated prevalences of 1.3 per million in Eastern and Central European countries for MKD, 5 per million in the Netherlands and 1 in a million in Europe for TRAPS (13, 14). FMF predominantly affects people from the Mediterranean Basin, including Turks, Non-Ashkenazi Jews, Armenians and Arabs, with estimated prevalences ranging from 1 to 2.5 per 1000 in Turkey, Israel and Armenia (13, 15). FMF patients have been much more rarely identified in other populations, where its prevalence remains largely unknown (15). The rarity of systemic autoinflammatory disorders and the variability of their initial symp-

toms can result in delayed diagnosis or misdiagnosis, which in turn lead to delayed treatment (16-18). Interleukin-1β (IL-1β) is a key mediator of inflammatory processes, and has been shown to play a pivotal role in the pathogenesis of various systemic autoinflammatory disorders including cryopyrin-associated autoinflammatory syndromes (CAPS), FMF, MKD, and TRAPS (19-24). Open-label studies have reported that IL-1β inhibition improves clinical and laboratory features in colchicine-resistant FMF (crFMF) (25-28), MKD (29) and TRAPS patients (30-32). The phase 3 CLUSTER trial demonstrated that canakinumab, a fully human anti-IL-1β monoclonal antibody, was highly effective in controlling and preventing flares in patients with crFMF, MKD and TRAPS (33). Here, we evaluate the effect of canakinumab treatment on the HRQoL in patients with crFMF, MKD or TRAPS with up to 41 weeks of treatment in the CLUSTER trial.

Methods

Study design

The phase 3 randomised CLUSTER trial (NCT02059291) had three disease cohorts including paediatric and adult patients with one of the following conditions: crFMF, MKD, and TRAPS. The detailed study design has been reported previously (33). The study included a screening period of up to 12 weeks (Epoch 1), a randomised, double-blind, placebo-controlled period of 16 weeks (Epoch 2), a randomised withdrawal period of 24 weeks (Epoch 3) and an open-label treatment period of 72 weeks (Epoch 4).

This manuscript presents HRQoL data obtained in Epoch 2 and 3 (*i.e.* from the start of the study to Week 40) in patients treated with canakinumab (150 mg or 300 mg every 4 weeks) during, at least, part of Epoch 2 and 3. According to the study design, patients randomised to placebo were started on treatment with canakinumab if the baseline flare was not resolved by Day 29 or if they experienced a new flare during Epoch 2, and therefore the precise period during which patients received canakinumab varied individually. Of the 185 patients enrolled in CLUSTER, 12 patients who were assigned to placebo were excluded from the analyses as they were never treated with canakinumab. Three of these patients discontinued the study during Epoch 2, and 9 had resolution of their baseline flare and did not experience any new flare during Epoch 2 on placebo, and therefore ended the study at the end of Epoch 2, as per protocol. HRQoL data were not collected during Epoch 4.

The institutional review board or independent ethics committee at each center approved the study. Written informed consent was provided by patients or guardians, as appropriate.

Patients

The detailed inclusion and exclusion criteria for patients have been reported previously (33). All patients were required to have active disease, with a flare at baseline (*i.e.* before starting Epoch 2), defined as Physician Global Assessment of Disease Activity (PGA) ≥2 on a 5-point scale and C-reactive protein (CRP) >10 mg/L. Other key inclusion criteria for crFMF patients were fulfillment of Tel Hashomer diagnostic criteria, at least one known *MEFV* exon 10 gene mutation, and historical data documenting ≥1 flare/month despite doses of colchicine (from 1.5 mg to 3.0 mg/day or equivalent paediatric age-/weight-adjusted regimen) or ≥1 flare/month with intolerance to effective colchicine doses. Patients on colchicine were requested to continue on a stable dose during the study. Key inclusion criteria for MKD patients included genetic or enzymatic diagnosis of the disease, and historical data documenting ≥3 flares in a 6-month period. For TRAPS patients, a *TNFRSF1A* gene mutation and chronic or recurrent (>6 flares/year) disease were required.

Assessments

HRQoL of patients with crFMF, MKD, or TRAPS was assessed at baseline, after 16 weeks (at Week 17, end of Epoch 2), and after 40 weeks (at Week 41, end of Epoch 3). The health status of patients treated with canakinumab across the three disease cohorts was assessed using three instruments: the Child Health Questionnaire – Parent Form 50 (CHQ-PF50) (34), the Short Form-12 (SF-12) Health Survey – acute version 2 (35), and the Sheehan Disability Scale (SDS) (36).

The CHQ-PF50 questionnaire was completed by the parents of patients with an age at baseline of >5 to <18 years, without input from the children. This questionnaire is normed for patients of 5–18 years and provides summary scores of "physical" and "psychosocial" health for 14 health status and well-being concepts: physical functioning, role/social emotional, role/social behaviour, role/social physical, bodily pain, general behavior, mental health, self-esteem, general health perception, change in health, parental emotional impact, parental impact on time, family activities, and family cohesion (37).

The SF-12 Health Survey (35) was completed by patients ≥18 years of age at baseline. SF-12 measures the impact of disease on overall quality of life and consists of 12 questions across subscales (physical function, pain, general and mental health, vitality, social function, and physical and emotional health). The subscales were aggregated to derive a "physical component summary score" and a "mental component summary score" (38). Both composite scores combine the 12 items in such a way that they compare to a US national norm mean score of 50.0 with a standard deviation of 10.0 (39).

To describe the variation on the HRQoL in the study population, percentages of patients who experienced an increase of >2 to 5, >5 to 8, and >8 points were calculated for each component of the CHQ-PF50 and the SF-12 scores. The 2, 5 and 8-point thresholds were arbitrarily chosen for descriptive purposes.

SDS (version 3) is a brief self-reporting tool to assess functional impairment in 3 inter-related domains: work/school, social life, and family life/home responsibilities. It was completed by patients >18 years and by the parents of paediatric patients. The patient rates the extent to which work/school, social life, or family responsibilities are impaired by their symptoms on a 10-point visual analog scale (VAS). This 10-point VAS uses spatiovisual, numeric, and verbal descriptive anchors simultaneously to assess disability. Each subscale, which

Table I. 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 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 at baseline			
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)

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

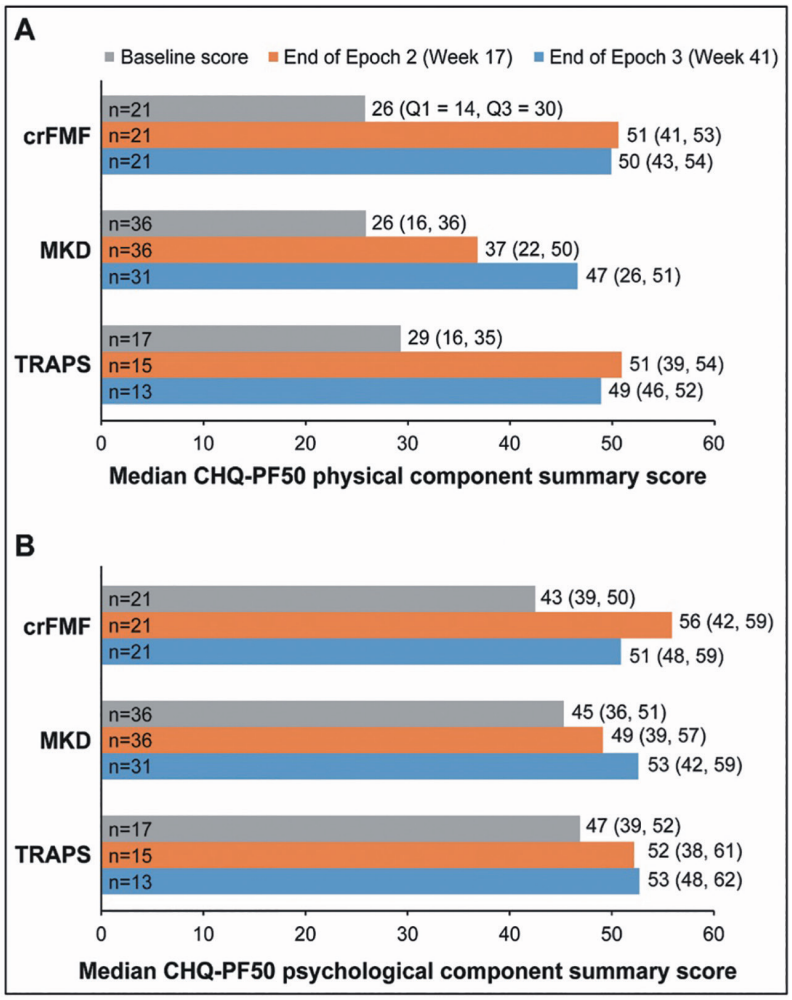

Fig. 1. Median (Q1–Q3) CHQ-PF50 physical (**A**) and psychological (**B**) component summary scores at baseline, Week 17 and Week 41 in paediatric patients (≥5–<18 years) treated with canakinumab. Analyses were done in patients that participated in Epoch 2 and 3 of the CLUSTER study (safety set). In each bar, n is the number of patients who received at least one dose of canakinumab and were evaluated for HRQoL.
CHQ-PF50: Child Health Questionnaire–Parent Form 50; crFMF: colchicine-resistant familial Mediterranean fever; HRQoL: health-related quality of life; MKD: mevalonate kinase deficiency; TRAPS: tumour necrosis factor receptor-associated periodic syndrome; Q1: first quartile; Q3, third quartile.

measures impairment of work/school, social life or family responsibilities, can be scored independently or can be combined into a single total score ranging from 0–30. A score of 0 represents unimpaired and 30 represents highly impaired in the scale. A score of 5 or higher in any of the scales is associated with significant impairment (36).

Statistical analysis

Analyses were performed in all patients who were exposed to canakinumab (including those initially randomised to placebo) during Epoch 2 (*i.e.* after flaring and before Week 17), and therefore continued the study to Epoch 3 as per protocol (*i.e.* up to Week 41). Results of HRQoL assessments were compared with baseline values for each individual. All data were analysed separately for each disease cohort (crFMF, MKD, and TRAPS). Descriptive statistics were used to summarise demographic and baseline characteristics, and also the results of all scores used at baseline, at the end of Epoch 2 and at the end of Epoch 3. Summary statistics for continuous variables included number of patients, median, and lower and upper quartiles.

Results

Demographic and baseline characteristics

Out of 185 patients enrolled in the CLUSTER study, 12 were excluded from this analysis as they did not receive canakinumab. Three of these patients (1 in each cohort) were randomised to receive 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 pro-

tocol. Demographic and baseline characteristics of the 173 patients included in this analysis are presented in Table I. Most patients (81-89%) were Caucasian and nearly 50% were males in the crFMF and TRAPS cohorts; 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, HIDS 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 60.0, 60.0 and 70.0 for patients with crFMF, HIDS and TRAPS, respectively.

CHQ-PF50 scores

CHQ-PF50 physical and psychological component summary scores in paediatric patients are presented in Figures 1A and B. Relatively low scores at baseline, particularly for the physical component, reflected the impact of the three diseases on the HRQoL of the patients. Most items and sub-scores of the questionnaire gave similar results in the three cohorts, except that patients with crFMF seemed to have worse results for the self-esteem score (median scores in a 0-100 scale of 66.7, 75.0 and 83.3 for patients with crFMF, MKD and TRAPS, respectively). At Week 17 (the end of Epoch 2), both physical and psychological scores increased, with values generally approaching to 50 and therefore comparable to those of the general population (39). This effect was maintained at Week 41, and no differences between cohorts were apparent.

SF-12 Health Survey scores

SF-12 physical and mental component summary scores in adult patients treated with canakinumab are presented in Figures 2 A and B. In general, results were comparable to those obtained in children using CHQ-PF50. Relatively low scores at baseline were observed particularly for the physical component, and sub-scores were similar between different cohorts except that patients with crFMF seemed to have worse values for the emotional health score (median norm-based scores of 32.5, 55.5 and 41.15 for patients with crFMF, MKD and TRAPS, respectively) and patients with TRAPS had worse values for the vitality score (median norm-based scores of 40.3, 40.3 and 31.1 for patients with crFMF, MKD and TRAPS, respectively). After 17 weeks of treatment, scores increased to values similar to those observed in the US national normal population, and improvements were generally maintained at Week 41, with no apparent differences between cohorts.

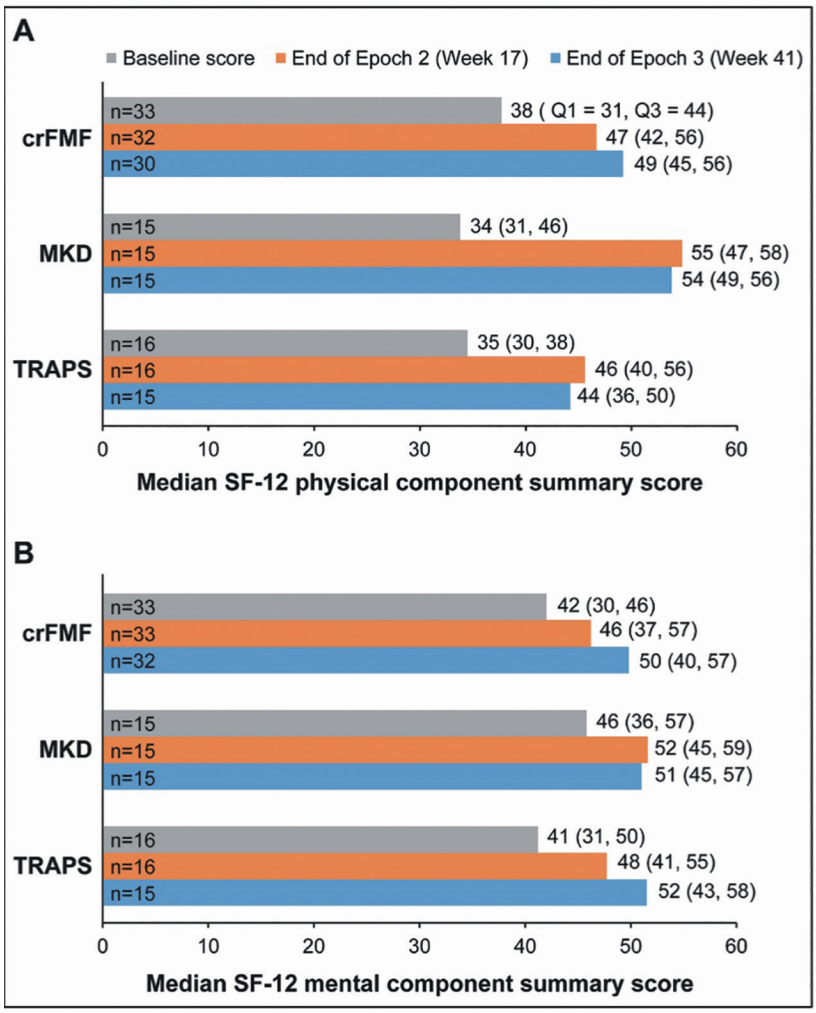

Fig. 2. Median (Q1–Q3) SF-12 physical (**A**) and mental (**B**) component summary scores at baseline, Week 17 and Week 41 in adult patients (≥18 years) treated with canakinumab.
Analyses were done in patients that participated in Epoch 2 and 3 of the CLUSTER study (safety set). In each bar, n is the number of patients who received at least one dose of canakinumab and were evaluated for HRQoL.
crFMF: colchicine-resistant familial Mediterranean fever; HRQoL: health-related quality of life; MKD: mevalonate kinase deficiency; SF-12: Short Form-12; TRAPS: tumour necrosis factor receptor-associated periodic syndrome; Q1: first quartile; Q3: third quartile.

SDS scores

SDS scores observed in canakinumab treated patients are presented in Figure 3. There was a decrease (improvement) in median SDS scores (global functional impairment, work/school, and social life) at Week 17 from baseline across all 3 disease cohorts (Fig. 3A-C). The improvements noted at Week 17 were generally maintained at Week 41 (Fig. 3A-C).

Percentages of patients experiencing improvements on HRQoL

The percentage of patients with increases in CHQ-PF50 and SF-12 scores of ≤2 points, >2-5 points, >5-8 points and

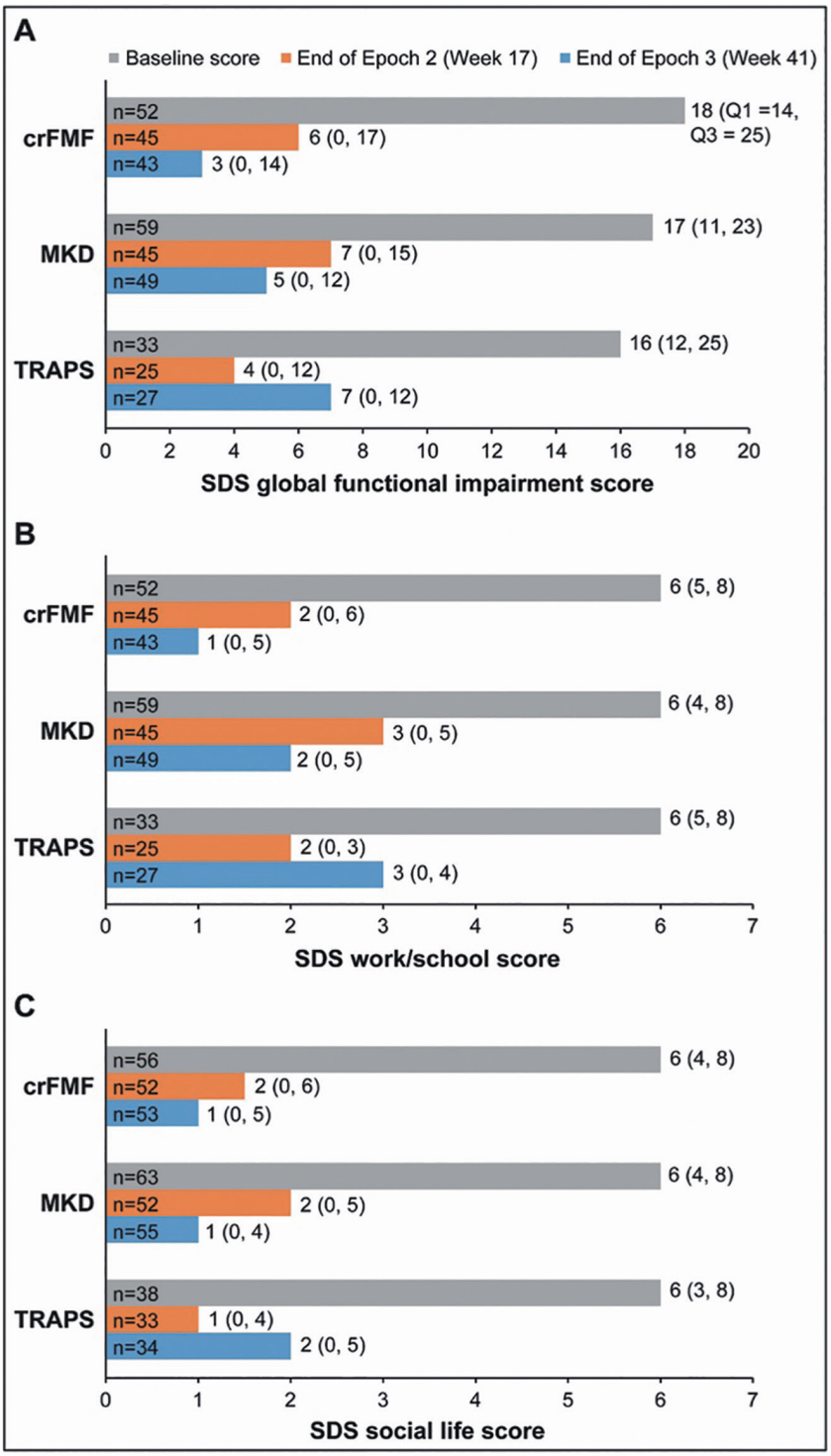

Fig. 3. Median (Q1–Q3) SDS scores for global functional impairment (**A**), work/school (**B**) and social life (**C**) at baseline, Week 17 and Week 41 for patients treated with canakinumab.
Analyses were done in patients that participated in Epoch 2 and 3 of the CLUSTER study (safety set). In each bar, n is the number of patients who received at least one dose of canakinumab and were evaluated for HRQoL.
crFMF: colchicine-resistant familial Mediterranean fever; HRQoL: health-related quality of life; MKD: mevalonate kinase deficiency; SDS: Sheehan Disability Scale; TRAPS: tumour necrosis factor receptor-associated periodic syndrome; Q1: first quartile; Q3: third quartile.

>8 points from baseline until the end of Epochs 2 and 3 are summarised in Figure 4. Between 44% and 87% patients experienced increases of more than 8 points in scores of physical HRQoL from baseline which were maintained to Week 41; this reflects a notable and sustained improvement. Even though baseline values for psychological/mental HRQoL were higher than for physical components, at least 30% of paediatric and adult patients with crFMF and MKD experienced sustained increases of more than 8 points in psychological/mental components.

Discussion

The burden of illness in patients with inadequately controlled systemic autoinflammatory syndromes is high. A patient-reported disease burden study of crFMF, MKD and TRAPS showed that disease flares have a significant negative impact on patients' and caregivers' physical, mental/psychosocial health and social functioning. This, in turn, adversly impacts patients' education and work achievements, leading to a reduced HRQoL and increased economic burden (40).

The primary results of the CLUSTER study showed that canakinumab was effective in rapidly and sustainably controlling disease activity and preventing new flares in patients with recurrent fever syndromes (33). Here, we used the data generated in the setting of the pivotal phase 3 CLUSTER trial to assess the HRQoL in patients treated with canakinumab. The present analysis provides a unique insight into the physical and psychosocial impact of crFMF, MKD and TRAPS on patients before and after treatment with canakinumab. Consistent with results on disease activity, in all three disease cohorts, a meaningful improvement in the quality of life during treatment with canakinumab was observed.

Since no validated tools are available for measuring HRQoL in both adults and children, we used different scores for paediatric patients (CHQ-PF50) and adults (SF-12). In addition, the SDS score was used for assessing the impact of disease in work/school, social and home life. In principle, the results obtained with these different generic tools cannot be compared. However a striking concordance was found across the data obtained with these different metrics. The similarity of the results obtained across these genetically dif-

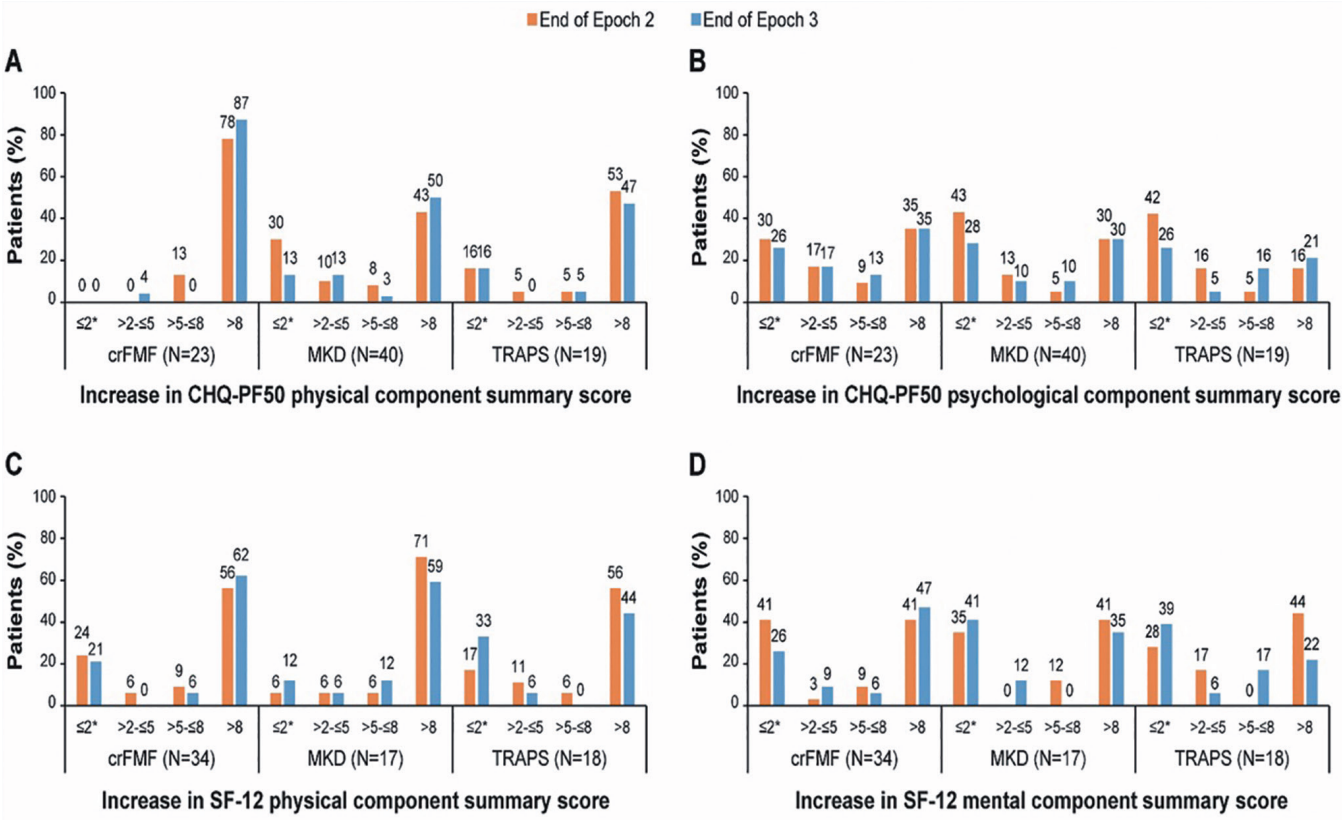

Fig. 4. Change from baseline in HRQoL scores measured by CHQ-PF50 (physical component, **A**; psychological component, **B**) and SF-12 (physical component, **C**; mental component, **D**).
The analysis included all patients from the safety set that received at least one dose of canakinumab. This number (N) was used as denominator to calculate the percentages, and is indicated for each cohort. Patients were classified according to their increases in the HRQoL summary component scores using arbitrary thresholds of 2, 5 and 8 points. The figure represents the percentage of patients experiencing increases in HRQoL scores of ≤2, >2–≤5, >5–≤8 and >8 points. Of note, patients experiencing no increases in HRQoL scores were included in the ≤2 category. Patients who either discontinued the study or for which no HRQoL data was available at some of the points were included in N, but not in any of the categories represented in the figure, for that reason, percentages do not generally add to 100.
crFMF: colchicine-resistant familial Mediterranean fever; HRQoL: health-related quality of life; MKD: mevalonate kinase deficiency; SF-12: Short Form-12; TRAPS: tumour necrosis factor receptor-associated periodic syndrome.
*Includes patients with no increase or increase ≤2.

ferent syndromes was also remarkable. Consequently, despite a weakness of the study in the use of generic assessments which have not been designed for these conditions, the consistency of the results obtained between paediatric and adult patients, across different tools, and in different autoinflammatory diseases; implies a robust and sustained improvement in general life experience by patients accompanying the clinical responses to canakinumab treatment reported in CLUSTER.

The low baseline values observed for the physical components of the CHQ-PF50 and SF-12 clearly reflected the impact of systemic autoinflammatory syndromes on physical aspects of HRQoL, when the disease is inadequately controlled. It should be pointed out that these patients had a high number of flares per year, and a median number of days with active disease ranging from 60 to 70 in the three disease cohorts. After 41 weeks, median scores clearly increased and approached the values expected in the general population, for both paediatric and adult patients of the three disease cohorts. Median baseline values for the psychological/mental components were also lower than for the general population, although not as low as for the physical components. This is consistent with previous reports on patients with CAPS (41). It is a bit surprising that, despite the high yearly number of days with fever, these patients reports a relatively low impact on psychological/mental components. It is tempting to speculate that patients affected by rare monogenic diseases with onset at very young age, such as the three syndromes studied here, may have become conditioned to be unusually accepting and stoicial in the presence of disease symptoms. Nonetheless with control of disease activity, there was an improvement in median scores to reach values similar to those observed in the general population.

In the present study, SDS scores at baseline were low, indicating that functional impairment can cause a considerable social and economic burden in patients. Observed improvements in the SDS global functional impairment scores (based on inter-related domains of work/school and social life) after 16 and 41 weeks were in line with those observed with the other HRQoL tools.

The design of the CLUSTER study means that a limitation of this analysis is

the lack of a control group of patients receiving placebo only. The analysis only included patients exposed to canakinumab, and comparisons were made between HRQoL scores at baseline and after canakinumab treatment in Epochs 2 and 3. The use of baseline values recorded when patients were experiencing a flare is another limitation of this study. Although most questions in HRQoL questionnaires ask about the status of the patient during a preceding longer period of time when the patients would not have been in flare, the perception of patients and parents is likely to have been affected by the current flare and this could potentially result in worse scores.

In conclusion, taken together, the results of this analysis indicate that patients with three inherited systemic autoinflammatory syndromes treated with canakinumab experience a meaningful improvement in physical, psychological, social and functional HRQoL. The persistent benefit over 41 weeks of the study suggests that these improvements are likely to translate into long-term real world experience.

Acknowledgements

The authors thank all investigators and patients for their participation in the study. The authors also thank Rajeeb Ghosh of Novartis Healthcare and Marco Migliaccio for medical writing assistance, which was funded by Novartis Pharma AG, Basel, Switzerland.

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