The burden of systemic juvenile idiopathic arthritis for patients and caregivers: an international survey and retrospective chart review

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Abstract

Objective

To investigate the burden of systemic juvenile idiopathic arthritis (SJIA) on health-related quality of life (HRQOL) and resource use of patients and caregivers (families) on biologic therapy.

Methods

This international study assessed SJIA burden in patients on biologics, using a caregiver questionnaire and retrospective chart review. Validated measures included: Child Health Questionnaire Parent-Form 50 (CHQ-PF50), 36-Item Short-Form Health Survey (SF-36v2) and Work Productivity and Activity Impairment questionnaire: Specific Health Problem (WPAI:SHP). Caregivers completed function, treatment satisfaction and resource utilisation questions.

Results

Sixty-one biologic treated patients participated (12 anakinra, 25 canakinumab, 24 tocilizumab). Mean age at diagnosis and survey completion was 6.4 and 11.3 years, respectively. Mean (±SD: standard deviation) CHQ-PF50 physical (PhS) and psychosocial (PsS) summary scores were significantly lower in SJIA patients than a normative population (PhS: 40.0±18.2 vs. 53.0±8.8; PsS: 46.6±11.3 vs. 51.2±9.1) as was caregivers' mean SF-36v2 mental component score (MCS; 46.2±10.7 vs. 50.0±10). Assistive devices were required by 54%; 20% required home/car alterations. According to caregivers, biologic treatment completely improved SJIA symptoms in 48% on canakinumab or tocilizumab and 32% on anakinra. Over 2 months, patients missed 2.9 school days due to SJIA (10% yearly loss). Caregivers lost 25 work days annually and 27.5 days of productivity (WPAI-SHP: mean absenteeism 10%; presenteeism 11%). Yearly SJIA travel/treatment costs averaged $1,130.

Conclusion

SJIA patients on biologic therapy experience HRQOL impairment, caregivers' mental well-being suffers and productivity losses and expenses are incurred. Therapeutic interventions that reduce the burden of SJIA are required.

Key words

Health-related quality of life, patient reported outcomes, systemic juvenile idiopathic arthritis, canakinumab, anakinra, tocilizumab

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Competing interests: see page 926.

Introduction

Previous publications indicate juvenile idiopathic arthritis (JIA) patients and their caregivers experience deterioration in health-related quality of life (HRQOL) (1-7). JIA patients incur direct costs for medications, medical visits, tests and hospitalisations and indirect costs including lost productivity and help from non-professional caregivers (1).

Systemic JIA (SJIA) is the most severe JIA category, representing approximately 5–15%, with an annual incidence in Europe of 0.3–0.8 cases per 100,000 children (8). SJIA appears to be an autoinflammatory disease involving activation of pro-inflammatory cytokines interleukin-1 (IL-1), IL-18 and IL-6 (9-12). It is distinguished from other JIA categories because it is characterised by arthritis and significant extra-articular systemic features including fever, evanescent rash, lymphadenopathy, hepatosplenomegaly and polyserositis (13). Canakinumab and tocilizumab, antibodies targeting the IL-1 and IL-6 receptor respectively, and anakinra, an anti-IL-1 receptor antagonist, have demonstrated efficacy in SJIA (14-16, 34). Canakinumab and tocilizumab have regulatory approval for treatment of SJIA. Optimising management remains challenging due to the heterogeneity of the disease and its response to treatment (17-19). Despite the severity of SJIA and treatment challenges, a detailed analysis of disease burden on patients and caregivers is missing.

In this international study, we evaluated caregivers' perspectives on the disease burden for children with SJIA receiving biologic treatment, using a cross-sectional caregiver questionnaire and retrospective chart review.

Patients and methods

Patient population and study design

This study was conducted at nine tertiary centres across the USA, France, Germany, Netherlands, and UK. Ethics committees in all centres approved the study protocol and written informed consent was obtained. Key inclusion criteria for patients were: 1) SJIA diagnosis based on International League of Associations for Rheumatology criteria (20) and 2) 4–18 years. Key caregiver inclusion criteria were: 1) care for an eligible child with SJIA for ≥6 months, 2) ≥50% time spent with the SJIA child, 3) ≥18 years. Patients were excluded if enrolled in a clinical trial changing their real-world experience. Caregivers with a psychiatric condition impacting their reliability were excluded. Eligible patients had received canakinumab, tocilizumab or anakinra for ≥2 months.

Measures

Physicians completed case report forms providing patient disease history and current status. Patients' Childhood Health Assessment Questionnaire (CHAQ), pain visual analogue scale (VAS) and global assessment VAS scores were provided where recorded (21). Demographic information and other components of burden were evaluated using a cross-sectional caregiver survey.

Caregivers provided their child's functional ability on a 4-point scale. Requirements for assistive devices and home or car alterations since SJIA diagnosis and in the past 4 weeks were collected.

The parent-administered 50-item version of the Child Health Questionnaire (CHQ-PF50) (22) assessed HRQOL of SJIA children compared to normative values. Caregivers' HRQOL was assessed using the 36-item Short-Form health survey (SF-36v2) (23). Caregivers' stress was assessed using an adapted version of the Pediatric Inventory for Parents (PIP) (24). Caregivers rated 14 SJIA-related items on two 5-point scales (frequency and stressfulness in the past 4 weeks).

Caregivers' satisfaction with anakinra, canakinumab and tocilizumab was evaluated using a tailored questionnaire based on entire treatment experience, regardless of current treatment. Treatment efficacy, convenience, associated anxiety, side-effects, burden, and compliance were assessed. Most questions used a 5-point scale ranging from 'not convenient' to 'extremely convenient', or equivalent. Efficacy was measured on a 6-point scale from 'no improvement at all' to 'complete improvement

Table I. SJIA patient/ caregiver demographics and patient functional status.

Participant demographics and patient functional status	n (%)* [N=61]
Patient characteristics	
Enrolment Site – U.S. : Europe	28:33
Female	29 (48)
Age at diagnosis – years†	6.4 ± 4.6 [55]
Prior or current corticosteroids†	40 (87) [46]
Prior or current methotrexate†	30 (65) [46]
Time from diagnosis to initiation of first biologic - years†	1.3 ± 2.6 [46]
Number of prior switches of biologic treatment†	0.7 ± 0.8 [46]
Age at survey completion – years	11.3 ± 4.5
Disease duration - years†	4.6 ± 4.0 [58]
Length of time on current biologic - years†	2.5 ± 2.3 [46]
First line biologic†	
Anakinra	31 (63) [49]
Canakinumab	5 (10) [49]
Tocilizumab	13 (27) [49]
Biologics received (at any time)©	
Anakinra	41 (67)
Canakinumab	29 (48)
Tocilizumab	31 (51)
Current biologic	
Anakinra	12 (20)
Canakinumab	25 (41)
Tocilizumab	24 (39)
Functional status	
CHAQ scores†	
Functionality [range 0-3]	0.3 ± 0.6 [42]
Pain VAS [range 0-10]	0.7 ± 2.0 [40]
Global assessment VAS [range 0-10]	1.3 ± 2.6 [38]
Impairment in past 4 weeks#	
Difficulty gripping objects	6 (10) [59]
Difficulty reaching for objects	8 (14) [59]
Difficulty standing up	6 (10) [59]

Participant demographics and patient functional status	n (%)* [N=61]
Assistive devices	
≥1 required since SJIA diagnosis	33 (54)
≥2 required since SJIA diagnosis	12 (20)
Wheelchair§	19 (58) [33]
Stroller§	15 (45) [33]
Walker/zimmer frame§	7 (21) [33]
Resting splints§	6 (18) [33]
≥1 required in the past 4 weeks	11 (18)
≥2 required in the past 4 weeks	5 (8)
Wheelchair◊	6 (55) [11]
Stroller◊	2 (18) [11]
Walker/zimmer frame◊	3 (27) [11]
Resting splints◊	2 (18) [11]
Home / Car / other alterations	
≥1 required since SJIA diagnosis	12 (20)
≥2 required since SJIA diagnosis	10 (16)
Toilet seat appliance§	5 (42) [12]
Bathtub/shower appliance§	8 (67) [12]
≥1 required in the past 4 weeks	6 (10)
≥2 required in the past 4 weeks	4 (7)
Toilet seat appliance◊	3 (50) [6]
Bathtub/shower appliance◊	3 (50) [6]
Stair lift◊	2 (33) [6]
Caregiver characteristics	
Female	48 (79)
Age at survey completion – years	41.2 ± 7.7
Number of dependents	2.4 ± 1.0
Single parent	11 (18)
Employment status	
Working, volunteering or studying full-time	28 (46)
Working, volunteering or studying part-time	22 (36)
Other‡	11 (18)
Academic degree¥	27 (44)
Number of medical conditions¤	1.0 ± 1.5

VAS: visual analogue scale.
* n: number and (percentage) unless otherwise specified. Plus-minus values are means±SD. [n=61] unless otherwise stated.
† Data taken from the chart review form. All other data collected from the caregiver survey.
# Level of difficulty assessed on a four-point scale from "Not difficult at all" to "Very difficult". Patients were classified as experiencing difficulty if caregivers answered "Moderately difficult" or "Very difficult".
§ Not all devices/alterations required are specified, only those required by ≥5 patients.
◊ Not all devices/alterations required are specified, only those required by ≥2 patients.
© Patients' prior and current biologic treatment are included. Caregivers could report that their child had received >1 biologic therapy. Patients received only one biologic treatment at a time.
‡ Includes stay-at-home parent (n=6), unemployed (n=2), retired (n=1), disabled (n=1) and within civil service (n=1).
¥ Defined as completion of undergraduate or postgraduate degree (U.K.); college degree or graduate degree (U.S.); Hochschulabschluss or weiterfuehrender Studienabschluss/Promotion (DE); HBO or Universiteit (NL); or diplôme de premier cycle or diplôme d'études supérieures (FR).
¤ Back problems (n=11), anxiety (n=6), hypertension (n=6), depression (n=5) and arthritis (n=5) were the most common conditions experienced by caregivers.

(no more symptoms)'. Compliance was measured on a 9-point scale from '1 in every 2' to '1 in every 10 or more' or 'no administrations were ever skipped'. Employed caregivers indicated on a 5-point scale how frequently and which SJIA related appointments caused them to miss work in the past two months. The number of days patients or their siblings missed school or required educational support due to SJIA were outlined. Additionally, caregivers completed the Specific Health Problem Work Productivity Activity Index (WPAI:SHP) (25), with SJIA-specific modifications (developer recommended). The WPAI:SHP has been used in rheumatoid arthritis (RA) (26).

Tailored questions assessed resource utilisation due to SJIA. Caregivers indicated the number of healthcare appointments and the number and type of appointments requiring overnight accommodation in the past two months. Caregivers specified the number of days their SJIA child or other dependents required a babysitter and if they or their partner required assistance from healthcare professionals in the past two months.

Additional treatment or travel related expenses incurred due to SJIA were collected. Caregivers specified the proportion of their family's expenses represented by SJIA-related costs and compared their family's SJIA-related expenses in the past two months to the previous year.

Statistical analysis

Descriptive statistics were reported as means and standard deviations (SDs)

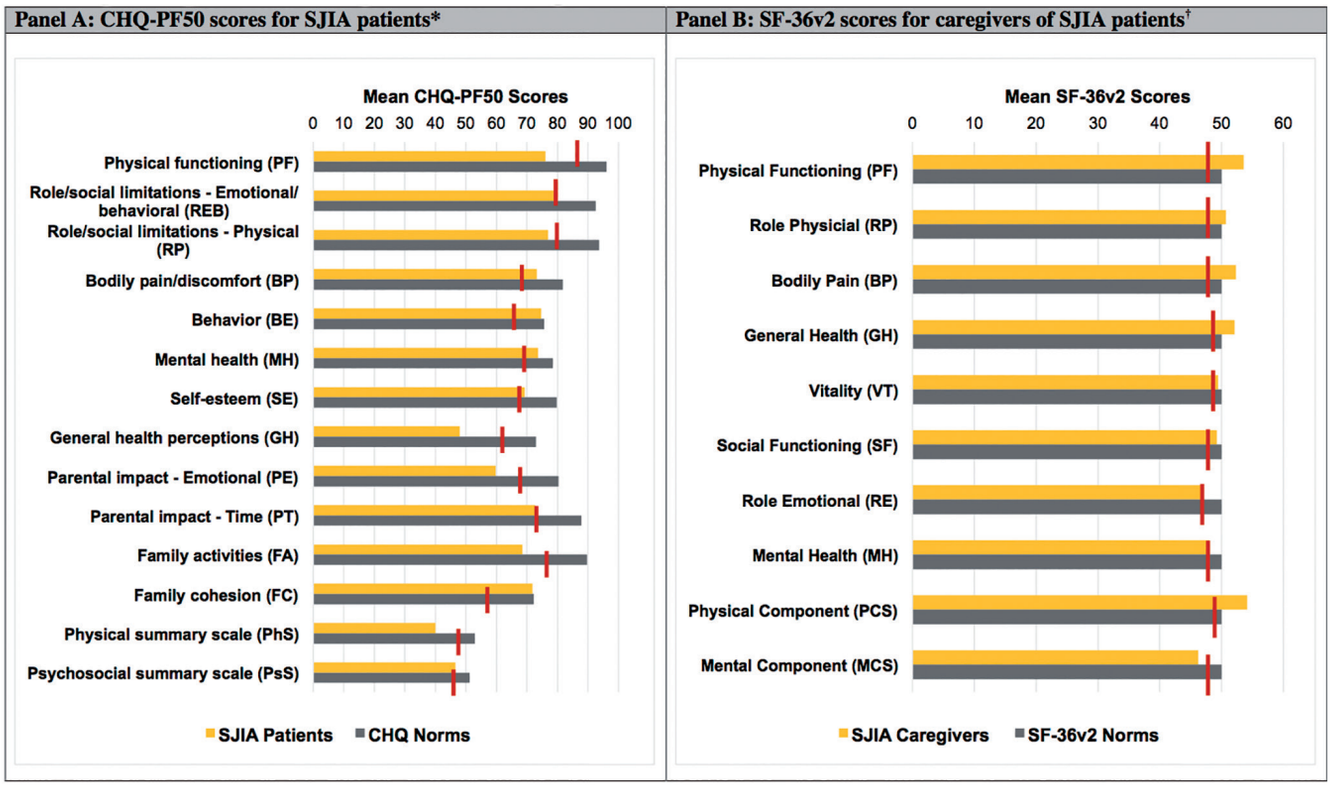

Fig. 1. HRQOL scores for SJIA patients and their caregivers.
* n=60; one caregiver did not answer the CHQ-PF50 section of the survey (reason unknown). Normative values taken from a sample U.S. population of 391 children, between 5 and 18 with a mean age of 11.5 years (30). Vertical bars represent -0.8 SD of the normative mean (a clinically important large effect size for the CHQ-PF50) (27).
† n=60; one caregiver provided their SF-36 responses after they had already been scored by the license holders
Normative values taken from a sample U.S. population (2). Red vertical bars represent a minimum clinically important effect size for SF-26v2 measures and scales (-0.3 SDs for MCS, PF, RP, BP, SF and MH, -0.2 SDs for PCS, GH and VT, and -0.4 SDs for RE) (23).

for continuous variables and absolute frequencies and percentages for categorical variables. Differences between biologically treated cohorts were assessed using Fisher's exact test and Kruskal-Wallis H test for categorical and continuous variables, respectively. Validated instruments were scored according to developers' guidelines. CHQ-PF50 scores were compared to a normative sample of 391 U.S. children aged 5-18 years (mean age 11.5 years) (30). CHQ-PF50 summary scores 0.2, 0.5 and 0.8 SDs lower than this normative population corresponded to a small, moderate and large effect size, respectively (27, 30). Norm-based SF-36v2 scores impaired by more than a minimal important difference (MID) compared to the U.S. population were indicated (MID values range 0.2–0.4 SDs) (23). The annual cost of WPAI-SHP calculated productivity loss was estimated using methods applied in osteoarthritis and RA studies, assuming an 40-hour week and 50 work weeks/year (29-30). Analyses were conducted using IBM SPSS Statistics 24 (IBM Corp. 2016).

Results

Participants

Sixty-one biologic treated SJIA patients were enrolled between June 2015 and June 2016 (France: 4; Germany: 12; Netherlands: 11; UK: 6; USA: 28). Patients' current treatments were anakinra (n=12), canakinumab (n=25) and tocilizumab (n=24).

The mean age of children at diagnosis and survey completion was 6.4 and 11.3 years, respectively. Corticosteroids and methotrexate were previously or currently used by 87% and 65% children, respectively. Mean time from diagnosis to first biologic treatment was 1.3 years. Mean disease duration and duration on current treatment at the time of survey completion was 4.6 years and 2.5 years, respectively. The mean age of caregivers was 41.2 years, 79% were female and 41% were working or volunteering full-time (Table I).

Functional ability

Mean (±SD) CHAQ scores were: 0.3±0.6 for functionality, 0.7±2.0 for pain VAS scale and 1.3±2.6 for global assessment VAS. Six (10%), 8 (14%) and 6 (10%) children found it difficult to grip objects, reach for objects and stand, respectively. Three children (5%) had difficulty with all three activities and 5 (8%) had difficulty in two of three activities.

An assistive device was required by 33 (54%) children, 20% required ≥2 devices, most commonly required were a wheelchair, stroller, walker/zimmer frame, and resting splints. Home, car or other alterations were made for 20%. Bathtub/shower and toilet seat appliances were the most common alterations. Most children (83%) required ≥2 alterations (Table I).

Table II. Treatment satisfaction of SJIA caregivers.

Caregiver treatment satisfaction	Anakinra n (%) [N][§]	Canakinumab n (%) [N][§]	Tocilizumab n (%) [N][§]	Treatment comparison (p-values)		
				Anakinra vs. canakinumab	Tocilizumab vs. canakinumab	Anakinra vs. tocilizumab
Treatment Satisfaction						
Therapy completely improved child's symptoms	13 (32) [41]	14 (48) [29]	15 (48) [31]	0.214	1.000	0.222
Therapy is/was convenient[†]	8 (20) [40]	20 (69) [29]	10 (32) [31]	<0.001	0.009	0.279
Child was extremely stressed/anxious receiving therapy	27 (66) [41]	3 (10) [29]	4 (13) [31]	<0.001	1.000	<0.001
Therapy was extreme burden	9 (22) [41]	2 (7) [29]	4 (13) [31]	0.108	0.672	0.371
Extremely stressed/anxious each time their child was given treatment for SJIA	14 (34) [41]	4 (14) [29]	2 (6) [31]	0.094	0.417	0.009
Extremely worried or concerned about the side effects of treatment	8 (20) [41]	6 (21) [29]	7 (23) [31]	1.000	1.000	0.777
Treatment adherence						
Patients who missed or skipped a treatment	6 (15) [41]	1 (4) [28]	6 (19) [31]	0.228	0.106	0.751
Reasons for skipping treatment[◊]						
Caregiver forgot to give the treatment	4 (67) [6]	1 (100) [1]	1 (17) [6]	1.000	0.286	0.242
Inconvenient for practical reasons	2 (33) [6]	1 (100) [1]	3 (50) [6]	0.429	1.000	1.000
Child forgot to take the treatment	3 (50) [6]	0 [1]	0 [6]	1.000	N/A	0.182
Existing side effects required temporary treatment stop	1 (17) [6]	0 [1]	1 (17) [6]	1.000	1.000	1.000
Worried about possible future side effects	1 (17) [6]	0 [1]	0 [6]	1.000	N/A	1.000
Hospital-related reasons	0 [6]	0 [1]	2 (33) [6]	N/A	1.000	0.455
Emotionally stressful for the child	1 (17) [6]	0 [1]	0 [6]	1.000	N/A	1.000
Other[¥]	2 (33) [6]	1 (100) [1]	3 (50) [6]	0.429	1.000	1.000

[§] Caregivers answered on the basis of any treatment experience with anakinra, canakinumab or tocilizumab received throughout the duration of their child's condition, irrespective of current treatment (*i.e.* caregivers of patients initiated on anakinra and switched to tocilizumab answered based on their experiences of anakinra and tocilizumab).
[†] Therapy was classified as convenient if respondents answered with "Somewhat convenient" or "Extremely convenient".
[◊] Caregivers could provide multiple reasons treatments were skipped. [¥] 'Other' reasons provided included: child was ill, child could not sleep and no refill.

HRQOL

Compared to normative data from a U.S. population, mean CHQ-PF50 PhS scores (40) for SJIA patients were lower by a large effect size and mean PsS scores (46.6) were lower by a moderate effect size (Fig. 1A and Supplementary Table S1) (27, 30). The most impaired concepts were general health perceptions, physical functioning, and parent impact-emotional.

Using the SF-36v2, caregivers displayed a higher mean physical HRQOL (PCS=54.1), although their mean mental HRQOL (MCS=46.2) was significantly lower (Fig. 1B and Supplementary Table S2).

Frequent and high causes of stress for caregivers were: 'worry about the long-term impact of their child's SJIA' (45%); 'uncertainty about the future of their child, family and themselves, due to their child's SJIA' (28%); and 'uncertainty about their child's ability to become fully independent as an adult' (27%) (Supplementary Table S3).

Assessment of biologic treatment

48% caregivers whose child had received canakinumab or tocilizumab, and 32% caregivers whose child had received anakinra, thought the treatment completely improved their child's symptoms (Table II). Significantly more caregivers thought canakinumab was 'convenient' (69%) *versus* anakinra (20%) or tocilizumab (32%) ($p<0.001$ and $p=0.009$, respectively). Significantly more caregivers thought their child was 'extremely stressed or anxious' receiving anakinra (66%) *versus* canakinumab (10%) or tocilizumab (13%) ($p<0.001$ for both). Significantly more caregivers were 'extremely stressed or anxious' when their child received anakinra (34%) *versus* tocilizumab (6%, $p=0.009$). Treatment was an 'extreme burden' for caregivers of 22% anakinra, 13% tocilizumab and 7% canakinumab treated children. Twenty-three percent, 21% and 20% caregivers were 'extremely worried or concerned' about the side-effects of tocilizumab, canakinumab and anakinra, respectively. We note that 22 and 9 caregivers had experience with two and three biologic therapies, respectively, which allowed them to compare attributes of multiple treatments when answering the questionnaire.

Treatment doses were missed by 1 (4%) canakinumab, 6 (15%) anakinra and 6 (19%) tocilizumab patients (Table II).

Productivity

77% caregivers were employed full- or part-time (Table I), however 36% had reduced their hours/stopped working due to child's SJIA (Table III). Six (11%) caregivers stated SJIA appointments caused them to miss work 'most of the time' or 'always' in the past two months. In the two months prior to survey completion, a mean of 2.9 school days were missed by patients due to SJIA (Table III). Assuming a 5-day school week and 36 school weeks/year, this equated to 10% yearly schooling loss.

Employed caregivers missed a mean of 2.8 hours of work in the past seven days due to their child's SJIA (absenteeism score: 10%) (Table III) which equated to an annual loss of 25 days (28-29). Caregivers' mean presenteeism (impairment at work) score was 11%, equivalent to a productivity loss of 27.5 work days (28-29). In total a

potential annual loss of 52.5 days was estimated, of which 48% was due to work days missed.

Resource utilisation

In the two months prior to survey completion, appointments commonly required were: visit to SJIA specialist (84%), visit to hospital/clinic for tests (69%) or for drug administration (64%) and telephone consult with SJIA specialist (34%).

Overnight accommodation for child's hospitalisation and drug administration was required by 20% and 15% of caregivers, respectively.

SJIA-related expenses represented ≥25% family expenses for 16% caregivers (Table IV). Compared to previous year, these expenses had increased for 15% caregivers. Travel and treatment costs were the most common recurrent expenses. Average yearly travel and treatment-related costs were $948 and $969, respectively.

Table III. Impact of SJIA on caregivers', patients' and other dependents' productivity.

Productivity Impact	n (%) [N][§]
Long-term (since SJIA diagnosis):	
Change in work commitments	
Reduced number of working hours	16 (26) [61]
Stopped working	6 (10) [61]
No change	39 (64) [61]
Short-term (in the past 2 months):	
School days missed due to SJIA– mean days±SD [N]	
Child with SJIA	2.9 ± 8.3 [60]
Other dependents[◊]	0.3 ± 1.5 [50]
Educational support required due to SJIA– mean days±SD [N]	
Child with SJIA	0.4 ± 1.5 [60]
Other dependents[◊]	0.5 ± 2.2 [49]
Caregiver often missed work due to SJIA appointments*[†]	6 (11) [54]
WPAI:SHP:	
Time missed due to child's SJIA over last 7 days* – mean hours±SD [N]	2.8 ± 6.6 [44]
Overall work impairment* - mean %±SD [N]	15 ± 27 [40]
Absenteeism* - mean %±SD [N]	10 ± 23 [42]
Presenteeism* - mean %±SD [N]	11 ± 22 [41]
Activity impairment - mean %±SD [N]	17 ± 26 [61]

[§] n: number and (percentage) unless otherwise specified. Plus-minus values are means±standard deviation.
* Only employed caregivers answered this question.
[◊] Only caregivers with other dependents answered this question.
[†] Caregivers were classified as often missing work due to SJIA appointments if they responded that they caused them to miss work "Most of the time" or "Always".

Discussion

This study provides the first analysis of caregiver perspectives on estimated healthcare utilisation, non-healthcare costs, productivity losses and treatment satisfaction of SJIA children on biologic therapy using surveys collected in the U.S. and five European countries. These data obtained outside the context of a clinical trial reflect real-world experiences.

Children enrolled had average disease duration of 4.6 years, approximately 1.3 years between SJIA diagnosis and treatment with first biologic and had received their current biologic for 2.5 years. Patients demonstrated functional limitation, as evidenced by their CHAQ scores and 10-15% patients had at least moderate difficulty gripping, reaching for objects or standing up. Despite this, the physical ability of many children displayed improvement – 22 (36%) required an assistive device at some point for their SJIA but not in the four weeks prior to survey completion. Frequently required assistive devices (such as wheelchairs, strollers, walking aids) highlight that functional impairment may be primarily driven by mobility restrictions.

This study suggests that SJIA patients on biologic therapy experience worse HRQOL compared to normative population, particularly in physical domains; consistent with previous results in JIA (2, 4), juvenile dermatomyositis (31) and RA (32). The use of varying patient- and proxy-reported measures to reach this outcome reinforces the result.

Our results indicate the areas of HRQOL impacted by SJIA are physical functioning, role/social limitations (physical), general health perceptions, parental impact (emotional) and family activities. Surprisingly, a large impact on bodily pain/discomfort was not observed. Patients' resilience to the threat to their well-being posed by SJIA and positive adaption to adversity may explain this (33-34). Behaviour and family cohesion sub-scores were similar to normative population, providing reassurance that despite children's physical limitations, their behaviour is not affected and family harmony remains strong.

Comparing CHQ-PF50 results from our study with those of Oliveira *et al*., suggests that SJIA patients experience an additional 4.5- and 1.1-point reduction in PhS and PsS scores compared with other JIA categories (4).

Impairment was similar to normative values in the parent emotional scales of CHQ-PF50 and SF-36v2 suggesting SJIA children impose an emotional toll rather than physical or functional impairment on their family. Bruns *et al*. similarly identified that the mental health of caregivers of JIA patients is one of the most impaired domains of HRQOL, based on SF-36 scores (3).

Canakinumab was found to be significantly more convenient than anakinra or tocilizumab, and anakinra caused significantly more patients and their caregivers extreme stress or anxiety. All biologic treatments were considered to impose a similar level of burden, side-effect concern and similar compliance. The stress and anxiety associated with anakinra may be attributable to its dosing and administration as a daily subcutaneous injection, and have been reported to have a high rate of injection site reactions, specifically pain (stinging and burning), rashes and swelling (35). Reducing caregivers' worry about the long-term impact of SJIA and uncertainty about the future for themselves,

Table IV. Resource utilisation and expenses.

Resource utilisation and expenses	n (%) [N=61]◊
Direct resource utilisation	
Appointments required in past 2 months*	
Visit to SJIA specialist	51 (84)
Visit to hospital/clinic for tests	42 (69)
Visit to hospital/clinic for drug administration	39 (64)
Telephone consult with SJIA specialist	21 (34)
Email consult with SJIA specialist	13 (21)
Visit to ophthalmologist / eye doctor	12 (20)
Visit to GP / family doctor	10 (16)
Visit to pediatrician	10 (16)
Other consultations required in past 2 months*	
Physiotherapist / occupation therapist	12 (20)†
Psychologist / counsellor	9 (15)†
Indirect resource utilisation:	
Appointments requiring arrangement of overnight accommodation since child has had SJIA*	
Overnight hospital stay	12 (20)
Visit to hospital/clinic for drug administration	9 (15)
Nanny/babysitter/child-minder required due to SJIA in the past 2 months – mean days±SD	
Child with SJIA	0.9 ± 4.1
Other dependents - [N]‡	0.6 ± 2.9 [49]
Caregiver or partner required healthcare assistance due to SJIA in past 2 months	14 (23)
Expenses:	
SJIA-related expenses	
≥25% of total family expenses	10 (16)
Increased compared to previous year	9 (15)
Decreased compared to previous year	11 (18)
Additional expenses – mean U.S. $ per year ±SD [N]¤	
Travel§	984 ± 1,610 [23]
Treatment¥	969 ± 800 [7]

GP: General practitioner.
◊ n: number and (percentage) unless otherwise specified. Plus-minus values are means±SD. [N=61] unless otherwise stated.
* Those required/incurred by ≥15% of patients listed.
‡ Caregivers with no other dependents specified 'N/A'.
§ Expenses classified as 'travel' include: Petrol/gas, train/bus/ferry tickets, parking fees.
¥ Expenses classified as 'treatment' include: insurance premiums, self-pay, drug costs and out-of-pocket/co-pay medicine.
¤ Expenses listed in U.S. $ based on exchange rate on 13 July 2016: €1 = $1.10572, £1 = $1.3249. Single or 'one-off' expenses not included.

their child with SJIA and their family is important.

Patients' direct healthcare resource use was high; in the two months prior to survey completion, 84% visited a SJIA specialist, 69% visited a hospital/clinic for tests and 64% visited a hospital/clinic for treatment. The productivity losses of biologic treated patients and their families are possibly explained by the volume of SJIA-related healthcare appointments required as well as periods of symptom-related incapacity.

Various authors have previously demonstrated that JIA poses a significant cost burden, primarily driven by the expense of medications (1, 36-37). Lapsley *et al*. identified total annual disease-related expenditures for RA at AU$1,513 (~$1,150) (38). In comparison, in our study, the out-of-pocket costs of SJIA patients on biologic therapy appear substantially greater – 15% SJIA patients and 20% caregivers required overnight accommodation at some point for drug administration. Average annual travel and treatment costs (including medication costs and co-payments) totaled $948 and $969, respectively.

On average, patients missed 10% school annually and their employed caregivers experienced absenteeism and presenteeism of 10% and 11%, respectively, leading to a potential annual work loss of over 50 days.

Strengths of this study include that it is the first to exclusively explore disease burden for biologic-treated SJIA patients and families using a relatively large international sample. Limitations of this study include its cross-sectional nature, proxy-reported HRQOL evaluation, reliance on U.S. population normative values, use of non-validated scales to evaluate treatment satisfaction and sampling from tertiary pediatric rheumatology centres. The latter poses particular challenges because access to specialist care and biologic treatments are highly variable; variance in resource utilisation and productivity costs between European countries have been identified in other rheumatic and arthritic diseases (1, 39). Future research among SJIA patients and their families should seek to identify and compare HRQOL and resource utilisation between countries and enable SJIA patients to self-report disease burden.

In conclusion, SJIA patients on biologic therapies have impaired HRQOL, particularly in physical domains, and their caregivers' mental well-being is impaired. SJIA families experience reduced school and work productivity and bear additional expenses. SJIA treatments can be a source of stress, anxiety and burden. These findings emphasise that prevention of physical disability is an important objective for SJIA treatment. There is a need for treatments that improve children's HRQOL, offer SJIA caregivers less emotional distress and limit disruption on SJIA families' school and work productivity.

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