Model Driven Paediatric European Digital Repository

Call identifier: FP7-ICT-2011-9 - **Grant agreement no**: 600932

Thematic Priority: ICT - ICT-2011.5.2: Virtual Physiological Human

Deliverable 5.4

Report on longitudinal data collection status

Due date of delivery: 28-02-2017

Actual submission date: 28- 02-2017

Start of the project: 1st March 2013
Ending Date: 31st May 2017

Partner responsible for this deliverable: IGG

Version: 1

Dissemination Level: Public

Document Classification

Title	Report on longitudinal data collection status
Deliverable	5.4
Reporting Period	3
Authors	IGG
Work Package	5
Security	Public
Nature	Report
Keyword(s)	Data collection, JIA

Document History

Name	Remark	Version	Date
Report on longitudinal data collection status		1	17/2/2017

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Abbreviations

IGG	**Istituto Giannina Gaslini**
JIA	**Juvenile idiopathic arthritis**
OPBG	**Ospedale Pediatrico Bambino Gesù**
UMCU	**University Medical Centre Utrecht**
USFD	**University of Sheffield**

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Introduction

This deliverable is a follow up on deliverable 5.3 and describes the enrolment of patients with juvenile idiopathic arthritis (JIA), baseline data collection, which was completed as per 31 December 2015 and the follow up of enrolled patients, which is continuing until the end of the project. Additionally, the deliverable discusses data processing and analysis steps that have taken place thus far.

Baseline data collection

As reported previously, patient enrolment was started in October 2013 for clinical partners IGG and OPBG, and in March 2014 for clinical partner UMCU. Enrolment ended in December 2015. In all three centres together, 169 patients have been enrolled (IGG: 75, OPBG: 64, UMCU: 30). Baseline data was available of 165 patients at the time of writing of Deliverable 5.3. Currently, updated information is available of all 169 patients and is reported in Table 1.

Table 1. Baseline data

	***N*=169**
Centre	
IGG, *n* (%)	75 (44.3)
OPBG, *n* (%)	64 (37.9)
UMCU, *n* (%)	30 (17.8)
Demographics	
Female, *n* (%)	126 (74.6)
Age at onset (y), median (IQR)	4.1 (2.3-7.7)
Age at diagnosis (y), median (IQR)	4.3 (2.5-7.9)
JIA onset	
Oligoarticular onset, *n* (%)	115 (68.1)
Polyarticular onset, *n* (%)	44 (26.0)
Psoriatic arthritis, *n* (%)	5 (3.0)
Enthesitis-related arthritis, *n* (%)	3 (1.8)
Undifferentiated arthritis	2 (1.2)
Disease characteristics	
ANA positive, *n* (%)	109 (64.5)
Rheumatoid factor positive, *n* (%)	0 (0)
HLA-B27 positive, *n* (%)	4 (2.4)
Uveitis, *n* (%)	11 (6.5)
Morning stiffness, *n* (%)	95 (56.2)
Disease activity	
Active joints (*n*), median (IQR)	2 (1-5)

Limited joints (*n*), median (IQR)	2 (1-4)
PGA, median (IQR)	5.0 (3.0-7.5)
Parent/patient assessment of pain, median (IQR)	3.0 (1.0-6.0)
Parent/patient assessment of well-being, median (IQR)	3.3 (1.0-5.8)
CHAQ score, median (IQR)	0.5 (0.1-1.0)
JADAS-71, median (IQR)	12.6 (7.9-18.2)
Laboratory	
White blood cells, median (IQR)	8.8 (7.0-11.1)
Neutrophils, median (IQR)	4.5 (3.5-5.5)
Lymphocytes, median (IQR)	3.0 (2.3-4.3)
Haemoglobin, median (IQR)	12.0 (11.3-12.7)
Platelets, median (IQR)	372 (299-468)
ESR, median (IQR)	23 (13-43)
CRP, median (IQR)	0.67 (0.45-2.0)
Medication	
Use of NSAIDs, *n* (%)	124 (73.4)
Use of other drugs, *n* (%)	33 (19.5)

Abbreviations: ANA, antinuclear antibodies; CHAQ, childhood health assessment questionnaire; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA, human leukocyte antigen; IGG, Istituto Giannina Gaslini; IQR, interquartile range; JADAS, juvenile arthritis disease activity score; JIA, juvenile idiopathic arthritis; NSAIDs, non-steroidal anti-inflammatory drugs; OPBG, Ospedale Pediatrico Bambino Gesù; PGA, physician's global assessment of disease activity on a 0-10 scale; UMCU, University Medical Centre Utrecht; y, year.

Baseline data collection consists in the collection of clinical data, such as demographics and disease characteristics, which has been collected of all enrolled patients. Likewise, blood samples for routine laboratory examinations (see Table 1) have been collected of all enrolled patients. Additional blood samples and, if available after joint injection, synovial fluid samples have been collected for Luminex® analysis. This has been done in 137 (81%) and 58 (34%) patients at baseline, respectively. Next, stool samples have been collected for the analysis of gut microbiota. In all, 121 samples (72% of patients) have been collected at baseline. Additionally, an extensive joint ultrasound was performed in 156 (92%) enrolled patients at baseline. Finally, imaging for the development of the biomechanical ankle model, i.e. MRI and CGA, was performed in patients with ankle involvement at baseline and aged at least 6 years. Furthermore, it was decided to include patients with long-term involvement of the ankle specifically for the ankle model as well. Currently, 26 patients have performed an MRI of the ankle at baseline (14 new-onset patients and 12 patients with long-term involvement of the ankle) and 24 of those have performed a CGA as well.

Follow up data

Patients are followed up every 6 months for 2 years after enrolment. Additional visits are performed if a patient presents with a disease flare.

At the time of writing of the report, the 6 months follow up visit has been performed for 161 (95%) patients, the 12 month visit for 149 (88%) patients, the 18 month visit for 120 (71%) patients and the 24 month visit for 89 (53%) patients. Additionally, 26 specific diseae flare visits have been performed in 24 (14%) patients.

As can be gleaned from the number of visits performed, not all patients will perform a 24 month follow up visit before the end of the project (31st May 2017). This is a consequence of a previous decision to continue patient enrolment until 31st December 2015. Nonetheless, all patients will have a 12 month visit (in fact, data collection at 12 months is almost complete now) and this is deemed a sufficient duration of follow up to identify predictors for the evolution of the disease.

At each follow up visit, disease status is monitored with respect to a) disease activity according to the internationally accepted and validated Wallace criteria, b) damage according to the juvenile arthritis damage index (JADI) and c) functional ability according to the childhood health assessment questionnaire (CHAQ). Disease status is summarized in Table 2.

Table 2. Disease outcome

	6 months (N=161)	12 months (N=149)	18 months (N=120)	24 months (N=89)
Clinical inactive disease	96 (60%)	111 (75%)	95 (79%)	67 (75%)
No functional limitations	106 (66%)	118 (79%)	96 (80%)	70 (79%)
No damage	150 (93%)	138 (93%)	114 (95%)	81 (91%)

Follow up data collection consists in the collection of clinical data, such as disease characteristics and outcome data (Table 2). An ultrasound exam is performed at 6 months of all joints that were involved at baseline, and at 12, 18 and 24 months only of the ankles if they were involved at baseline. Blood and synovial fluid for Luminex® and stools for microbiota analysis are collected if a patient presents with clinical inactive disease, or a disease flare. CGA is performed at 6 and 12 months of all patients who performed CGA at baseline and the ankle MRI is repeated at 12 and 24 months. Additionally, a lower limb MRI is performed at 6 months. See Table 3 for follow up data collection and Table 4 for the performance of MRI and CGA.

Table 3. Follow up data collection

	6 months (N=161)	12 months (N=149)	18 months (N=120)	24 months (N=89)
Blood sample[1]	69 (43)	75 (50)	55 (46)	44 (49)
Synovial fluid sample[1]	11 (7)	4 (3)	3 (3)	3 (3)
Stool sample[1]	61 (23)	48 (32)	30 (25)	28 (31)
Ultrasound[2]	135 (84)	80 (54)	53 (44)	43 (48)

[1] According to protocol only collected in case of inactive disease or disease flare.
[2] According to protocol performed at 6 months; at 12, 18 and 24 months only if the ankle was involved at baseline.

Table 4. MRI and CGA

	New-onset		Long-term		Total	
	MRI	CGA	MRI	CGA	MRI	CGA
6 months	10	9	9	9	19	18
12 months	9	6	7	7	16	13
24 months	8	-	1	-	9	-

Data processing and analysis

All collected data has been uploaded to the MD-Paedigree data platform and is available for the consortium partners. Baseline and follow up data are currently being processed and analyzed in various ways.

First, all CGAs and MRIs have been anonymized and uploaded to the platform. These are currently being elaborated by USFD (WP10) for the biomechanical ankle development and Fraunhofer (WP10) for the automated MRI segmentation tool. The work is carried out in close collaboration with the clinical partners. Manual segmentation of the MRIs has been performed of selected MRIs by the radiologists of the two clinical parnters UMCU and OPBG, to validate the automatic segmentation algorithm, developed by Fraunhofer. A meeting was organized in January at IGG, where all partners involved in the data collection and analysis convened, to discuss all cases and the results of the ankle models produced thus far, as well as strategies to go forward from there.

Secondly, baseline stool samples have been sent to OPBG (Lorenza Putignani, WP7). DNA was extracted and qualitatively and quantitatively characterized for next generation sequencing (NGS) gene-targeted metagenomics. DNA has been stored into the OPBG bio-bank. The samples have been included into a DNA subset, also including DNA extracted from healthy children, used as controls (OPBG bio-bank) in an age-, gender- and geography-matched case-control design. Due to expected difference between Italian and Dutch children, UMCU collected healthy-control stool samples in a 1:1 age and gender-matched design.

In order to analyse the operational taxonomic unit (OTU) content of JIA patients, a targeted approach based on pyrosequencing of the variable regions V1 and V3 of the 16S rRNA locus have been performed. Qualitative and quantitative metagenomic analyses of gut microbiota OTUs at Phylum and Order level have been provided, including the bioinformatic elaborations of JIA gut microbiota type, described by weighted/unweighted UNIFRAC and Bray Curtis algorithms.

Next, baseline blood and synovial fluid samples have been sent to partner UMCU and Luminex® analysis was performed. A second batch, containing most of the follow up samples will be sent to UMCU and analyzed in due time.

These microbiota and laboratory data have been matched with clinical and imaging data, obtained during the visits. A comprehensive database has been constructed, which was sent to partner UoA for statistical analysis, consisting of development and validation of prediction models for the evolution of the disease. This work is being carried out in close collaboration with clinical partners IGG, OPBG and UMCU, who provide clinical background information regarding the various data sources as well as clinical use cases. At the time of writing of this report, preliminary models have been developed, showing promising results, however needing further refinement.

Next to this integrative data analysis, pieces of data are being analyzed separately. Microbiota results of baseline, inactive disease and persistent activity samples for Italian and Dutch patients have been compared to healthy controls. This analysis shows remarkable differences between patients and healthy controls at all time points, potentially pointing towards a role of microbiota in the pathogenesis of JIA. This is the first large, longitudinal cohort of patients with diverse geographical background concerning gut microbiota in JIA to be published. It is expected that the paper will be submitted soon.

The ultrasound data, acquired according to a standardized protocol, is of interest to validate this imaging modality in JIA. Interesting questions include the clinical relevance of so-called sub-clinical findings, the presence of ultrasound abnormalities in the absence of clinically apparent arthritis. Other questions pertain to the definition of ultrasound abnormalities in the various joints and the predictive ability of this imaging modality in JIA. These analyses are being carried out by partner OPBG.

Finally, analysis of baseline Luminex data is on its way as well. Almost 80 cytokines and chemokines are being analyzed in a large and well defined cohort of JIA patients at baseline. Results are still preliminary, but indicate associations with disease activity for various cytokines. When Luminex® results of follow up samples will be available (in the next month), these results will be aggregated to the baseline data and differences across various disease activity states will be explored. Correlations between Luminex® and microbiota data will be explored as well.

Conclusion

As the end of the project nearers, data collection for WP5 draws to an end. Collected data are of high quality and show an overall good completeness. Data analysis has commenced more than a year ago, using preliminary data, and is progressing with ever more complete data sets as the project continues. Over the next couple of months, prior to the end of the project, we expect to perform the last laboratory analyses, continue the statistical analyses and start writing articles about our findings.