

## 1.0 Abstract

### Title

Assessing Long-term Effectiveness of Adalimumab for treating children and adolescents with Crohn's disease in real life conditions – LEA.

### Keywords

Adalimumab, Crohn's disease, observational study, pediatrics.

### Rationale and Background

In pediatric patients, the reported incidence rates of Crohn's disease (CD) ranges from 0.1 to 13.9 per 100,000 persons internationally. Besides intestinal and extra-intestinal manifestations, growth failure and pubertal delay are specific to children and adolescents with CD, involving up to 30% of children and challenging their quality of life. CD therapies aim to reach sustained, steroid-free remission, with mucosal healing and enhancement of growth and pubertal development of pediatric patients. Apart from enteral nutritional therapy, oral corticosteroid, and aminosalicylates, anti-TNF treatments are indicated in CD pediatric patients. In particular, adalimumab demonstrated efficacy and tolerability up to 52 weeks in an interventional study conducted in 192 children and adolescents with active CD. However, long-term outcomes were only available in CD adults treated with adalimumab and no data were available in treated pediatric patients.

### Research Question and Objectives

At the time of the protocol writing, the primary objective of this study was to evaluate long-term effectiveness of adalimumab in pediatric patients starting a treatment for CD in real-life conditions, namely to describe the time to loss of clinical benefit in a time to event approach. Main secondary objectives were to describe growth and pubertal development and to describe long-term safety. The patients were to be followed for up to 10 years.

Considering the limited number of inclusions during the planned 2-year period (n=62 versus 200 expected) and in agreement with French Health Authorities, the study discontinued prematurely on 14/10/2019, with very few follow-up medical visits after 12 months. Consequently, analysis focused on the baseline characteristics of pediatric patients who started treatment with adalimumab for Crohn’s disease, the use of adalimumab and safety data collected until Month 12 (M12). Exploratory objectives aimed to describe available effectiveness data and evolution of treated patient productivity.

### **Study Design**

This was a French prospective, non-interventional, multicenter study conducted in pediatric patients who started adalimumab treatment with for CD in real-life conditions. Follow-up visits, treatments, procedures and diagnostic methods were at the sole discretion of the participant physicians. Data to be documented in a dedicated eCRF were those closest to the following time-windows: baseline, 3, 6 and 12 months after, and then every year until the end of the study. At each study visit, physicians asked patients to fulfil a “paper” questionnaire on their productivity (at school or work whichever was applicable).

The initially planned study duration was 12 years (inclusions: 2 years; follow-up: 10 years). Considering the limited number of enrolled patients at the end of the inclusion period, the study was prematurely discontinued at that time.

### **Setting**

Overall, 10 gastroenterologists, involved in the management of pediatric patients and usually prescribing adalimumab for CD, participated in this French study. First patient entered the study on September 24, 2017 and last inclusion was performed on August 07, 2019; last patient last visit was on October 14, 2019.

### **Subjects and Study Size, Including Dropouts**

#### Selection criteria

#### Inclusion criteria

- Patient aged between 6 and 17 years old
- Suffering from Crohn’s disease
- Adalimumab-naive patient (a patient having received an anti-TNF other than adalimumab may enter the study)
- Starting a treatment with adalimumab
- Guardian capable of and willing to grant authorization for use/disclosure of data collected and patient able to comply with the requirements of the study protocol

#### Exclusion criteria

- Patients with a history of treatment with adalimumab
- Patients enrolled in a concomitant interventional clinical trial

#### Study size

Around 200 included children and adolescents starting adalimumab for CD were initially expected over a 2-year period; 62 were enrolled during this time with none of them being excluded from analysis.

#### **Variables and Data Sources**

##### Variables

Considering the changes in study conduct as described above, the planned analyses related to the long-term outcomes of adalimumab were not performed.

The following analysis were carried out:

- Baseline characteristics of eligible patients, medical history, CD characteristics, and prior CD treatments
- Modalities of the use of adalimumab (number and percentage of patients with each drug regimen during the initial and the maintenance treatment periods, treatment duration, number and percentage of patients with temporary discontinuation(s), number and percentage of patients with permanent discontinuation with reasons, concomitant treatments for CD and other diseases)

- Number and percentage of patients with at least one serious adverse event (SAE), with at least one adverse event of special interest (AESI), with at least one serious AESI, with at least one SAE (AESI, serious AESI) leading to permanent discontinuation of treatment, with at least one SAE (AESI, serious AESI) leading to death (and detailed adverse events); causal relationship with adalimumab and outcomes.

Exploratory effectiveness variables were as follows growth and puberty data, CD activity, imaging and laboratory data (at each follow-up visit until M12).

Data from the work productivity questionnaire completed by patients at each follow-up visit until M12 were other exploratory variables.

#### Data sources

Data were prospectively collected by investigators. Patient's source data were patient's medical records.

In addition, patients were asked to complete self-reported questionnaires on their productivity at each study visit.

## **Results**

### Baseline patient and CD characteristics

The mean age of patients was 13±3 years at inclusion, ranging from 6 to 17 years according to the product label for pediatric CD. The majority of them were female patients (60%) and lived in urban area (74%). All patients had never smoked at inclusion and one of them was consuming alcohol. A growth delay was diagnosed in 18/54 patients (33%).

Apart from CD, 47% of patients had past or concomitant diseases and 23% at least one concomitant disease at the time of inclusion [mainly as respiratory, thoracic and

mediastinal disorders (7%, asthma for all) and congenital, familial and genetic disorders (5%)]. Family history of IBD was reported in 19% of cases.

The mean age of patients was 12±3 years at CD diagnosis. At this time, according to the Paris classification, the main CD locations were ileocolonic (44%) and colonic (32%), and the most reported phenotype was the non-stricturing and non-penetrating one (90%).

At inclusion, the median disease duration from first CD symptoms was 1.5 year (range: 0.1; 9.1). At least one past or ongoing CD complication was reported in 52% of patients, mainly as anal fissures (31%), stenosing lesions (13%) or perineal fistulae (10%). At inclusion, 27% of patients had at least one CD complication, including 13% of patients with anal fissures and/or 10% with stenosing lesion. At least one past or ongoing extra-intestinal manifestation was observed in 26% of patients, mainly as acute peripheral rheumatism (16%) and erythema nodosum (7%). At inclusion, 11% of patients had at least one extra-intestinal manifestation, including acute peripheral rheumatism (5%) and erythema nodosum (5%).

Distal ileum and left colon (transverse – left – sigmoid – rectum) were the most locations affected by CD (in 71% and 41% of the cases, respectively). Stenosis and intraperitoneal abscess were reported in 4 and 1 patients, respectively.

At inclusion, the mean wPCDAI score was 32.1±24.0; it was 3.7±4.1 for the HBI, and 12.6±8.0 for the SES-CD. According to the wPCDAI, the proportions of the patients with moderate (score: [40; 57.5]), severe (score ≥57.5), and then moderate-to-severe (score ≥40) disease activity were 17%, 17%, and 35%, respectively. According to the HBI, the proportions of the patients with moderate (score: [8; 16]), severe (score >16), and then moderate-to-severe (score >16) disease activity were 14%, 0%, and 14%, respectively. In the other hand, using SES-CD, 59%, 24%, and 83% of patients had moderate (score: [7; 15]), severe (score >15), and then moderate-to-severe (score >7) endoscopic activity respectively at inclusion. The majority of patients had CRP value >10 mg/L (59%), and high fecal calprotectin value (≥100 µg/L: 81%, ≥250 µg/L: 71%).

Using the work productivity questionnaire completed at inclusion, 4 patients (7%) did not attend school due to CD. Two patients (4%) went to school as part-time due to CD, and 30 patients (56%) missed school for a total of 5 days or more over the 6 last months.

#### Prior and concomitant therapies

The majority of patients (73%) received at least one previous CD treatment, mainly as azathioprine (39%), corticosteroids (31%), and/or infliximab (27%), as well as enteral nutrition (37%). In 66% of patients, at least one CD treatment was prescribed in combination with adalimumab during the study period, mainly as azathioprine (44%) and/or corticosteroids (31%). Two patients (3%) underwent at least one surgery for CD before inclusion and the same number had surgery during the study period.

#### Use of adalimumab

Adalimumab was mainly prescribed as second-line treatment, after failure of conventional treatment or first anti-TNF (24% and 16% of patients, respectively), and in the case of poor tolerability of current treatment (11%) or contra-indication of conventional therapy (5%). It was used as anti-TNF of first intention in 27% of patients.

As planned by the investigators, compliance to the adalimumab label was observed for the majority of patients: 74% at treatment initiation, 68% at maintenance therapy, and 56% at both times. Similar compliance was observed during follow-up (in 80% of patients at M3, 83% at M6, 80% at M12, and 79% at all times).

During patient follow-up (median duration: 6.7 months; range: 0.0 ; 21.8), 7 patients (11%) stopped adalimumab permanently, mainly due to the lack (n=2) or loss of efficacy (n=2), and to related AE (n=2). The few temporary treatment discontinuations (3 patients, 5%) were due to infections (n=2) and/or patient poor observance (n=2).

#### Exploratory effectiveness analysis

Between treatment start and M6, CD activity decreased by wPCDAI (decrease of at least 37.5) in 27% of patients (7/26). wPCDAI remission (score <12.5) was reached at M3 and M6 in 70% (23/33) and 73% (22/30) of patients, respectively. HBI remission (score <5) was reached at M3 and M6 in 96% (48/50) and 98% (39/40) of patients, respectively.

Improvement in CRP value was also observed during follow-up [ $\leq 10$  mg/L: 41% at inclusion (20/49), 85% at M3 (40/47), and 77% at M6 (26/34)].

Regarding the evolution of patient work productivity between inclusion and M6, the proportion of patients with missed school for a total of 5 days over this period decreased from 57% (30/53) to 22% (7/32).

#### Safety data

Only AESIs and SAEs were required to be reported by investigators after the first adalimumab injection.

From inclusion and during patient follow-up (median duration: 6.7 months; range: 0.0 ; 21.8), at least one AE was reported in 13 patients (21%, 18 events reported) and 7 patients (11%) experienced at least one AE assessed as related to adalimumab (9 related AEs including 4 CD flares or digestive ulcers)

At least one SAE was reported in 10 patients (16%, 12 SAEs reported) and 5 patients (8%) experienced at least one SAE related to adalimumab (6 related SAEs with the preferred terms: CD, colitis ulcerative, ileal ulcer, drug-induced liver injury, malnutrition, and arthralgia).

Five AEs reported in 5 patients (8%) led to treatment discontinuation. Among these 5 AEs, 4 events were assessed as related to adalimumab (CD, drug-induced liver injury, malnutrition, and arthralgia).

One patient (2%) experienced one serious AESI related to adalimumab (probable drug-induced hepatitis) that led to treatment discontinuation.

No malignancy or fatal AE was reported.

### **Discussion**

Currently there is limited French real-world data on pediatric patients starting adalimumab for CD. The LEA study was set up to close this data gap. Due to the limited number of included patients (n=62), the study discontinued prematurely and only exploratory effectiveness analysis was performed until M12. Finally, the LEA study mainly aimed to describe the characteristics of treated CD pediatric patients, as well as the use and the safety profile of adalimumab.

The characteristics of pediatric patients included in the LEA study were broadly similar to previous non-French interventional and observational studies. At adalimumab start, only 35% of patients had moderate-to-severe disease activity at inclusion by wPCDAI (moderate: 17%; severe: 17%), whereas 39% were mild and 27% were inactive. However, moderate-to-severe endoscopic activity was observed in most patients (83%; moderate: 59%; severe; 24%) using SES-CD, with high CRP (60% > 10mg/L) and high fecal calprotectin (80%  $\geq$  100  $\mu$ g/L; 70%  $\geq$  250  $\mu$ g/L which indicate an active disease.

Adalimumab was mainly prescribed as second-line treatment, after failure of conventional treatment (24%) or first anti-TNF (16%), and in the case of poor tolerability of current treatment (11%) or contra-indication of conventional therapy (5%). Treated patients were aged between 6 and 17 years according to the product label for pediatric CD. In the majority of the cases, adalimumab regimens were in accordance with the product label at initiation and maintenance therapy.

Adalimumab was well tolerated with a low number of SAEs and 8% of patients discontinuing treatment prematurely for safety reasons. No new safety signals were detected.

In addition, our findings tend to confirm in a real-life setting the efficacy of adalimumab in CD children and adolescents as CD activity decreased by wPCDAI (at least 37.5) in 27% of patients. wPCDAI remission (score <12.5) and HBI remission (score <5) were reached at M3 in 70% and 96% of cases, respectively, and at M6 in 73% and 98% of patients. CRF decrease was also observed after adalimumab initiation ( $\leq 10$  mg/L: (rom 41% at inclusion to 85% at M3 and 77% at M6).

Overall, considering the lack of French data in pediatric CD patients treated with adalimumab, the present study provides new information in this context, both reassuring on the use and on the safety profile of adalimumab.

#### **Marketing Authorization Holder(s)**

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