Interreg CENTRAL EUROPE
Focus IN CD
European Union
European Regional Development Fund

ACTIVITY A.T3.2 IMPLEMENTATION OF PILOT PROJECT

D.T3.2.6 “Detecting and managing CD patient within a 'cohort of super allergic population” Pilot project Final Report

1. RESULTS ACHIEVED ACCORDINGLY TO OBJECTIVES

- **Please review the objectives you have set up in your D.T3.1.1 description, in the Status report Phase 1 and describe activities and results achieved by your pilot. Give an overview of the processes that are part of your pilot project.**

We have preliminary data confirming that super allergic patients have an increase frequency of CD, By putting together different expertise such as allergologists, GI and biotechnologist our aim was to speed up patients' collection and analysis to confirm data. This study had the aim to identify a new clinical condition at risk of CD, which calls for screening in other hospitals within the region and to other health care institutions in order to prevent possible complications of untreated CD.

Our Pilot project "Detecting and managing CD patient within a 'cohort of super allergic population" comprises 3 topics:

1- Evaluate the prevalence of celiac disease in children with very severe food allergy, undergoing specific food oral immunotherapy (OIT).

Patients were included in our study according to the following criteria: elevated IgE levels against food proteins (IgE values > 85 kU/l) and a positive history of at least one severe allergic reaction (i.e., a reaction defined as classes 4 and 5 according to Clark's classification) after accidental or voluntary (oral challenge) exposure to the causal food.

One the partner, as a reference centre for allergy in the region, has collaborated to identify patients and provide samples for screenig.

During the period of activity of the pilot project we have enrolled a total of one hundred and twenty children (72 M, 48 F, mean age 10±3 years) with very severe food allergy (98 with cow's milk allergy, 48 with egg allergy, 15 with wheat allergy).
Serum samples were analyzed
- for IgA anti-endomysium antibodies (AEA) by indirect immunofluorescence on cryostat sections of human umbilical cord,
- IgA-IgG anti-TG2 antibodies were measured using an ELISA (Eurospital, Trieste, Italy) following the manufacturer's instructions (normal values <7 U/l).
- The susceptibility alleles for CD were determined by PCR with allele-specific primers identifying HLA DQ2 and DQ8, using Eu-Gene-Risk kit (Eurospital).
Intestinal biopsy was recommended to subjects testing positive to both the serologic and the genetic tests, so as to obtain definitive diagnosis of CD.

Endoscopy was done and small bowel biopsies showed mucosal intestinal atrophy. All patients were placed on GFD.
The immune assays and biopsy analysis were performed by operators blinded to the subjects' clinical and laboratory data.

At the end of the study we find that Nine subjects (9/120, 7.5%, 6 M, 3 F) with severe food allergy tested positive for both the serological CD markers (AEA and anti-tTG), and HLA DQ2/8 haplotypes.

The results obtained so far reinforce the idea that active screening of celiac disease is necessary among those with severe allergy and that this practice should be included in the pediatrician clinical activity.

2 Collection of information regarding clinical symptoms, laboratory data, and OIT outcome from the newly diagnosed celiac patients both before and after diagnosis, to investigate whether the gluten-free diet (GFD) had any effect on the allergic manifestations.

Clinical and laboratory data were collected regarding the newly diagnosed cases of CD, and eventual changes before and after GFD were correlated.
The prevalence in the study group was compared with that of 128 age-matched children (68 M, 60 F, mean age 11±2 years) who had made a spontaneous recovery from food allergy without OIT and also with a control group made up of 3188 healthy schoolchildren screened for CD in Trieste, in these last two groups the prevalence was equal to 1%.

Specific IgE, IgG4 and the tolerated dose were measured before and after OIT and no differences were observed between patients with only severe food allergy and patients with both severe food allergy and CD.

More specifically, with regard to children allergic to cow's milk, in eight untreated CD patients (before diagnosis), four treated CD patients (on GFD for more than 12 months), and 40 non-celiac allergic patients, we measured the minimum trigger dose to induce severe symptoms before oral immunotherapy and the maximum tolerated milk dose 10 days after oral immunotherapy. No statistical differences were found among these three groups regarding the cow's milk-tolerated doses, with no differences among untreated and treated CD patients (P = 0.8).

3) Sharing of the knowledge of severe allergy and CD clinical connection among HCP in northeastern Italy.

- Results: we have organized several scientific meetings where we have illustrated both the general idea of the project FOCUS in CD as well as the pilot project for the diagnosis of CD in super allergic population. More significant were **two meetings with over 500 pediatricians and family doctors from our region (Grado 11 October 2018) and Veneto (Treviso 16 November 2018)** dedicated to improving the knowledge regarding the diagnosis and follow-up of celiac disease.

2. ADDED VALUE OF THE DEVELOPED & TESTED PILOT SOLUTION IN YOUR REGIONAL ENVIRONMENT

- Please describe shortly, what is the gained added value for the end-user of pilot service solution

ADDED VALUE for END-USER	
Short term effects	**Long-term effects**
1. We have identified a new group at risk of celiac disease and diagnosed celiac patients that were unaware of their disease condition. Our screening will help them to better manage their condition, to gain knowledge of the disease, to reduce problems and disorders complications risks thanks to a strict diet compliance.	1. We have confirmed that a specific population of patients (super allergic) have a higher risk of presenting as associated disorder CD. This will lead, by the help of HCPs and stakeholders, to share new CD-diagnostic guidelines.
2. We have shared our knowledge on the allergy/CD relation with pediatricians and allergologists of the region that are now able to recognize and manage these new CD related clinical conditions.	2. We have established a stable presence of stakeholder groups on this specific field that will allow the diffusion of the knowledges acquired during this project and at the end better quality of life of allergic/celiac disease patients

3. DEVIATION AND PROBLEMS ENCONTERED

- **In case your outcomes are different from the planned, please give an explanation of the reasons and formulate your modified results achieved. Was your planned model working or did you had to make modifications, if yes, describe ? Did you had any problems in you pilot implementation? If yes, which was the solution adopted?**

We have successfully reached all intended outcomes of our pilot. Collaborations within the two projects partners involved help to achieve all tasks planned.

The only relative problem encountered during the project was due to possibility of accessing very large numbers and diversity of samples to be tested. This limit as to be seen in terms of:

- absolute numbers of patients tested. During the pilot we limit the number of patients by working only with the one accessing directly to the PP7 hospital clinical allergy service

- limited variability of the patients selected especially in term of ethnic origins.

These limits, now that we have positively validated the model could be easily overcome by a multicentre/multinational study.

4. LESSON LEARNED RELATED TO CO-CREATION OF PILOT SOLUTIONS WITH ENGAGED STAKEHOLDERS

- Please describe what were the benefits and setbacks related to co-creation of pilot project with stakeholders.

LESSONS LEARNED	
Benefits	Setbacks
1. The merge of basic research and daily clinical practice (both in the clinical allergy service as well as in the gastroenterology one) has force both partners to have frequent interactions and share mutual feedback on clinical results and patient's follow-up. This has strengthened a stable collaboration that has substantial advantages for both the patients as well as for all the staff involved.	1. There were no specific setbacks in our project
2. The close collaboration within the stakeholders ie the regional allergological group, the center for research in autoimmunity (in Novara -Italy) and PP5 and PP7 has created a scientific network with wider connections (national and internationals) that will help in disseminating out the outcomes and guidelines produced.	2.

5. FURTHER ACTION PLAN (ACTIVITIES FOR THE FUTURE)

- What are your further activities of the pilot project development,
  - On the local level ?
  - On transnational level ?

On the local level ?

Our main aim is to maintain strong interactions within the stakeholder group that is constituted by pediatricians, allergologist, gastroenterologists and applied biology/immunology researcher.

We plan to have one or two annual meetings within the discussion group to share clinical cases and share innovations on CD-diagnostic methods.

On transnational level ?
we aim to present our data that link severe allergy and celiac disease to colleagues both in other "working groups" as well as in scientific societies working in the same field (CD and Allergy) to increase awareness and knowledge about our pilot project discovery. Data from this study will be presented at the ESPGHAN annual meeting in Glasgow 5-8 June 2019 as a poster presentation (A-1071-0003-01001).

- How did you plan to ensure sustainability to your pilot? Have you plan any action for the maintenance/follow up/development of the actions implemented, after the project ends?

- Sustainability:

  - the idea behind the pilot project (find a link between sever allergy and CD) was verified by a working group (paediatricians, allergologists, gastroenterologists and researcher) that was born during the project, but that as single units continue to operate continuously even after the end of the project. Therefore, no problems are foreseen to continue a future collaboration in this specific field which is part of the normal therapeutic diagnostic institutional activities.

  - The availability of Guidelines acquired by the pilot clinical and diagnostic experience will allow to diffuse the knowledge and the application of the screening procedure for CD diagnosis by other working groups so to become a hopefully standard diffuse procedure.

  - Sustainability can be foster by application to other competitive research grants in the future

- *Transferability and cooperation:*

  - Deliverable D.T3.3.1 "Transnational transferability plan of pilot solutions" -

  - Deliverable D.T3.3.2 "Pilot project recommendations for transfer to other users/regions"

  Based on feedback from pilot stakeholder and by using our clinical and scientific network with plan to transfer our diagnostic protocol to other possible users within the consortium participating regions as well as to extra projects regions.

  - e-tools will be promoted as well.