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Executive Summary

Within WP1, thanks to a previous and ongoing effort of the ESID registry, as well as the IUIS, a cohort of >200 patients with inborn errors immunity (IEI) and confirmed SARS-CoV-2 infection has been established. This cohort has served as the basis of extensive further research on the specific cohorts with IEI at risk for severe COVID19 and/or the development of anti-type I IFN alpha autoantibodies.

Abbreviations

D	Deliverable
DOA	Declaration of the Action
EC	European Commission
GDPR	General Data Protection Regulations
WP	Work Package
WT	Work Task

Contents

1 COVID-19 in Inborn Errors of Immunity Cohorts

1.1 Patients with IEI at risk of severe COVID19

- Patients with inborn errors of type I IFN immunity (such as STAT2 deficiency PMID: 36976641, IFNAR1 deficiency) are at increased risk of developing critical COVID19 and served as a model for the study of underlying causes of critical COVID19.

- Through a meta-analysis, we found that among infectious causes of death in patients with IEI, COVID19 accounted for 10%.

- Persistent symptoms after COVID-19 are prevalent among patients with IEI, with various risk factors identified, including underlying IEI, such as non-agammaglobulinemia antibody deficiency.

- The study of patients with various clinical phenotypes of COVID19 disease have allowed the UNDINE consortium to establish novel Inborn Errors of Immunity with specific (COVID19) or more general (respiratory viral infections) increased risk for severe / critical viral infection: FIP200 deficiency (PMID: 41309545), inborn errors of OAS1, RNAseL deficiency (PMID: 36538032) BTNL8 deficiency (PMID: 39576310) etc. Also, novel, previously unknown or underreported phenotypes of well-known IEI were described by the study of IEI such as the increased susceptibility to severe COVID19 in patients with MYD88 / IRAK4 deficiency (pubmed 36880831).

- The study of patients with APECED by AIRE mutations, harboring AAB-IFN-I, and suffering from critical COVID19, led to the hypothesis that these auto-abs would play a pathogenic role.

Several other cohorts of patients with IEI demonstrate impaired peripheral tolerance with propensity to producing AAB-IFN-I:

* Complete PTCRA deficiency leads to impaired thymocyte development and can underlie AAB-IFN-I among a wide spectrum of autoimmune phenotype

* The study of RelB deficiency showed that these patients are at risk of severe viral and COVID19 infection by the presence of neutralizing AAB-IFN-I. (PNAS 2024) Seven of the eight tested patients had AAN-I-IFNs correlating with their severe viral disease.

* Female patients with Incontinentia pigmenti have thymic dysplasia underlying AAB-IFN-I in a third of patients and are at high risk of severe viral diseases.

Next to these published observations, there is ongoing work which will continue after the final reporting date: potentially, patients with G6PDH deficiency suffer from MIS-C in the context of COVID19. In addition, patients with human ADA2 deficiency are at risk of critical COVID19.

Additional examples where the study of IEI cohorts has led to increased insight in the pathogenesis of critical COVID19 for the general population, can be found in the respective WPs.

2 Conclusion

The study of COVID19 in cohorts with Inborn Errors of Immunity have served as a window on the pathophysiology of the risk of critical COVID19. New gene defects have been included as IEI based on their susceptibility for viral infections (either COVID19, other viruses or a general predisposing condition).

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