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Safety and feasibility of intradermal injection with tolerogenic dendritic cells pulsed with proinsulin peptide-for type 1 diabetes

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injection. Grade 1 adverse events such as fatigue were noted in two patients receiving the lowest tolDC dose in the time period between leukapheresis and tolDC injection. Two patients showed decreased leucocytes and mild eosinophilia in the intermediate dose group, and dry skin and arthralgia were noted in one patient in the highest dose group (appendix p 9). Registered events had resolved in the monitoring period without requiring additional intervention. Finally, minor deviations from the reference range in blood chemistry were registered (appendix p 9) at the last monitoring appointment and appeared to be reversible, and not part of any morbidity as shown outside of the study follow-up.

β -cell function and overall diabetic control remained stable during the 6 months of extensive monitoring. All patients maintained tight glycaemic control after tolDC treatment with stable HbA_{1c} values, unchanged insulin requirements, and a similar number of weakly hypoglycaemic events as before the trial, until the last follow-up visit (figure 1B). This finding was irrespective of the administered tolDC dose. Residual β -cell function was assessed by a mixed-meal tolerance test before and after the tolDC injection. Of the nine patients included in the study, three had detectable stimulated C-peptide that did not change after tolDC treatment. This low rate of residual β -cell function was expected given our safety-driven strategy of choosing only patients with long standing type 1 diabetes (on average more than 12 years with the disease) for this first-in-man trial.

Prime-boost intradermal vaccination containing up to 20 million proinsulin-epitope loaded tolDCs per injection coincided with low grade, acceptable toxicity which was not likely related to the therapy. Most importantly, there were no signs of systemic immune suppression, no induction of allergy to insulin, no interference with insulin therapy, and

no accelerated loss in β -cell function in patients with the remaining C-peptide. In conclusion, generation and intradermal administration of autologous tolDCs pulsed with proinsulin peptide appears feasible and safe. Our results warrant subsequent clinical testing in patients with a shorter diagnosis of type 1 diabetes and with preserved C-peptide production, to assess whether this novel immune intervention strategy is able to delay or halt progressive loss of β -cell function. Further testing would tell whether antigen-specific immunomodulation using tolDCs protects β cells from autoimmune destruction and can act as curative therapy for type 1 diabetes.

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Use of glucocorticoids in patients with adrenal insufficiency and COVID-19 infection

In March 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease (COVID-19), reached pandemic level with a high global mortality rate.¹ The initial immune response to viral load is followed by an uncontrolled cytokine storm with hyperinflammation and immunosuppression. In the patients who are critically ill, infected alveolar epithelial cells trigger the release of inflammatory cytokines, which activates fibroblasts. Subsequently, uncontrolled viral propagation induces cytotoxicity and hyperactivation of immune cells. The cytokine storm leads to increased clotting, vascular inflammation, thromboembolism, and hypotensive shock.

Glucocorticoids have both stimulating and inhibitory effects on the immune response. In the initial phases of an infection, physiological glucocorticoid concentrations help to prime the immune system. In turn, this response activates the hypothalamic–pituitary–adrenal (HPA) axis to mild immunosuppression to reduce autoimmunity and cytokine toxicity. In critical illness (eg, COVID-19 pneumonia), HPA activation might be blunted, leading to corticosteroid insufficiency related to critical illness.²

The rationale for use of glucocorticoids in lung damage lies in their

ability to reduce inflammation and, ideally, fibrosis. However, the absence of benefit on overall survival has discouraged their use³ to the point that WHO guidance on management of COVID-19 advises against corticosteroids, unless indicated for other reasons.⁴ Adrenal insufficiency is one of those reasons and standard care suggests to apply the so-called sick day rules when COVID-19 is suspected.⁵

Patients with adrenal insufficiency have an increased risk of infection due to their depleted innate immunity, characterised by increased monocytes and decreased cytotoxic natural killer cells,⁶ which could facilitate the worsening of a SARS-CoV-2 infection into severe acute respiratory distress syndrome. Given the role of the HPA axis in stress priming the immune response, patients with adrenal insufficiency are intuitively at high risk of infection, especially as corticosteroid therapy during infection is still largely tailored empirically, often disregarding timing and dosage. The rationale of the more the better avoids risking inadequate concentrations of corticosteroids. However, mild COVID-19 symptoms such as fatigue, malaise, gastrointestinal symptoms, and diarrhoea are common in patients with adrenal insufficiency, and patients' fears might lead them to increase their dose unnecessarily. Establishing the correct timing of stress dose administration relative to the degree of inflammatory damage and the desired effect on the immune system is crucial—ie, not too early, not too late.

Given that hydrocortisone clearance decreases with stress, in mild symptomatic COVID-19 it seems safe to replace the missing stress-induced cortisol rise with additional doses (at least doubling the original regimen). In cases of persistent fever or progression of respiratory damage to severe pneumonia, an initial bolus of 50–100 mg of hydrocortisone followed by continuous intravenous infusion of 200 mg of hydrocortisone would be the most appropriate

replacement for patients with adrenal insufficiency.⁷ Such regimen can reduce the harmful effects of peaks and troughs of hydrocortisone on the immune system,⁷ and the length of stay in an intensive care unit.⁸ Hydration and electrolyte balance should also be corrected promptly, as severe hypotension is very frequent with disease progression. There is also increasing concern over the disseminated thromboembolic disease observed in severe COVID-19. Given the coagulation abnormalities associated with glucocorticoid use, low molecular weight heparin should be introduced early.⁹

In summary, tailoring of glucocorticoid stress regimens in COVID-19 requires a more evidence-based approach. The pathophysiology of immune response and the systemic complications associated with a SARS-CoV-2 infection set the pace, and the protocol should be adapted to the patient's clinical stage.

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Managing diabetes in Qatar during the COVID-19 pandemic

The coronavirus disease 2019 (COVID-19) pandemic has immediate implications for people with diabetes. Diabetes diminishes immune function, which contributes to a higher risk of severe COVID-19 infection requiring intensive care and a higher fatality rate than is associated with people who do not have diabetes.^{1–3} Glycaemic control can also be challenging with COVID-19, placing more burden on a fatigued health-care system. Simultaneously, people with diabetes cannot receive standard care because of resource diversion towards COVID-19. Key challenges for diabetes care during the pandemic include reduced access to health care, education, investigations, monitoring supplies, medications, and vaccinations. Furthermore, isolation measures result in increased food intake, reduced physical activity, irregular schedules translating to glycaemic

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