SUMMARY

Graft versus host disease (GvHD) is a common and severe complication which affects about half the patients who have been treated with allogeneic bone marrow transplantation. It occurs when the transplanted immune system from the donor recognizes the healthy cells of the patient as foreign cells. This generates an immunological attack on the healthy cells. There is an acute form which typically occurs within a few months from the transplantation. It develops fast and may involve the skin, gastrointestinal tract or liver. Acute GvHD is characterized by acute inflammation and can rapidly evolve into a life-threatening condition.

The chronic form of GvHD occurs later, develops slowly and resembles many known autoimmune diseases such as Sjögrens syndrome, systemic scleroderma, auto-immune biliary cirrhosis and immune cytopenias.

The most common approach to treatment of GvHD is to inhibit the immune response in different ways. For both acute and chronic GvHD the first-line treatment is corticosteroid in large doses, often combined with a calcineurin inhibitor, mycophenolate mofetil or sirolimus. Unfortunately, this is not sufficiently effective in approximately half of the patients. Many different drugs have been investigated as treatment options but evidence of their efficacy is derived mainly from small, retrospective, uncontrolled studies. It remains unknown which treatment is superior. Furthermore, it is difficult to compare these studies due to differences in criteria for and timing of response assessment. The included patient populations are very heterogeneous and have been treated with many different drugs prior to or concomitant with the drug of interest.

In study I, we evaluated the results of treatment with the tumour-necrosis-factor alpha inhibitor infliximab which has been used for second-line treatment of aGvHD since the year 2000. Until 2014, 68 patients received this therapy. With this treatment, a complete or almost complete remission of all symptoms of aGvHD was achieved in 46% of patients 28 days after first administration of infliximab. Nevertheless, a significant problem with insufficient control of aGvHD and severe infections remained for more than half the patients. Only 34% of patients were alive two years after start of treatment.

In study II, we investigated how disease activity of cGvHD changed during and after treatment with extracorporeal photopheresis (ECP). In ECP, leucocytes are collected from the patient’s blood by apheresis, treated with 8-methoxypsoralen (8-MOP), and exposed to ultraviolet light.
The treated cells are returned to the patient where they undergo apoptosis within 24-48 hours. This is thought to alter the immune reaction in a more anti-inflammatory direction which potentially dampens the GvHD reaction.

We evaluated response in 54 patients for up to three years after start of ECP as cGvHD typically has a long and fluctuating course. We found that 61% of patients overall experienced improvement of symptoms but also that approximately half the patients experienced periods with worsening symptoms and/or need for additional therapy.

In study III, we investigated the effect of the latest strategy for treatment of corticosteroid-resistant aGvHD, where ECP was added to the existing treatment with infliximab. Overall, we found that response rates after 7 and 28 days were comparable to those of infliximab alone but in total there was a response in 82% of patients treated with ECP. Patients who begin ECP concomitant to infliximab had better response rate on day 28 compared to those who received ECP later.

The three studies contribute with evaluations of the effect of therapy at standardized time points facilitating comparison with previous and future studies. For cGvHD there is also a description of the fluctuations which occur continuously during ECP. An unmet need for better treatment and randomized, controlled trials to evaluate treatment effect remains.

**Study I:**
*Evaluation of infliximab as second-line treatment of acute graft versus host disease -validating response on day 7 and 28 as predictors of survival.*

**Study II:**
*Longitudinal follow-up of response status and concomitant immunosuppression in patients treated with extracorporeal photopheresis for chronic graft versus host disease.*

**Study III:**
*Extracorporeal photopheresis is a valuable treatment option in steroid-refractory or steroid-dependent acute graft versus host disease-experience with three different approaches.*
Nygaard M, Karlsmark T, Andersen NS, Schjødt IM, Petersen SL, Friis LS, Kornblit BT, Sengeløv H. Bone Marrow Transplant. 2018 Jun 15. doi: 10.1038/s41409-018-0262-x. [Epub ahead of print]