Two heads are better than one: a synergistic strategy for conquering graft-*versus*-host disease

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Lastovytska *et al*. have combined extracorporeal photopheresis (ECP) and ruxolitinib to treat acute graft-*versus*-host disease (aGvHD) and compared the response to a group of patients receiving ruxolitinib alone.[1] Glucocorticoids are the first-line therapy for aGvHD and chronic GvHD (cGvHD), with response rates of 40-60%, which indicates that potent second- and third-line therapies are essential.

The authors have combined two approaches with very different mechanisms of action. ECP induces immunomodulation in diseases mediated by pathologic auto-/alloreactive T cells. Anti-inflammatory effects of ECP were recently shown to rely on the phagocytosis of apoptotic immune cells resulting in the production of adiponectin in the inflamed organ.[2] While not yet approved by the US Food and Drug Administration or the European Medicines Agency for this indication, ECP is broadly used in steroid-refractory a/cGvHD. Conversely, ruxolitinib interferes with Janus-associated kinases (JAK) 1 and 2 activation, which reduces signaling of multiple cytokine receptors.[3] Ruxolitinib decreased the frequency of pathogenic T cells, e.g., $CD4^+IFN\text{-}\gamma^+$ and $CD4^+IL17A^+$ cells[4] and MHC-II surface levels on dendritic cells[5] in mice developing GvHD. In a murine model of cGvHD, ruxolitinib treatment reduced collagen deposition in the lungs and improved pulmonary function.[6] A randomized, open-label, multicenter clinical trial of ruxolitinib compared to best available therapy (BAT) for corticosteroid-refractory or -dependent cGvHD (REACH-3; clinicaltrials.gov identifier 03112603) randomized 329 patients to receive either ruxolitinib 10 mg twice daily or one of 10 investigator-selected BAT.[7] The overall response rates at week 24 after treatment start were higher in the ruxolitinib group compared to the BAT.[7] The improved failure-free survival rate in the ruxolitinib group was also seen at a 3-year follow-up.[8] Although response rates up to 59% can be achieved in patients with steroid-refractory aGvHD with ruxolitinib, around 18% of the patients have a secondary failure of ruxolinib and/or need an additional immunosuppressive drug for aGvHD management. Thus, Lastovytska *et al*.[1] investigated synergistic effects of a combined second-line treatment with ruxolitinib and ECP (RUX/ECP) for SR-aGvHD in a retrospective analysis. While short-term response rates were higher in the ruxolitinib monotherapy arm, significantly more patients had a sustained (complete) response one year after therapy initiation with RUX/ECP.

A major observation made by the authors was that patients treated with RUX/ECP for aGvHD also had lower rates of cGvHD. This is consistent with aGvHD being a major risk factor for cGvHD. In accordance with the results of the authors, it was shown that RUX/ECP for patients with refractory cGvHD yielded response rates over 65% in a retrospective case study.[9]

A major clinical problem in patients with cGvHD is lung involvement because effective treatment and biomarkers for response to corticosteroids are lacking. A recent study showed that treatment with dexamethasone up-regulated the expression of total glucocorticoid receptor in patients with chronic obstructive pulmonary disease that responded to treatment, but not in non-responders.[10] Preventing cGvHD of the lungs by the use of RUX/ECP for initial aGvHD, as described by Lastovytska *et al*., may be a strategy to reduce this severe complication. Furthermore, Lastovytska *et al*. also showed that patients treated with RUX/ECP had a superior composite endpoint cGvHD and relapse-free survival after 12 months, and significantly more patients in the RUX/ECP arm had completely tapered any immunosuppressant. Both, cGvHD and the intake of immunosuppressive drugs negatively impact on quality of life. The combination of drug-blocking kinases that mediate cytokine and growth factor signaling with a tolerance-inducing approach that relies on apoptotic cells causing macrophage reprogramming and adiponectin production is novel and innovative (Figure 1).

A major concern of immunosuppression in GvHD patients is safety, in particular infections and relapse rate. Although

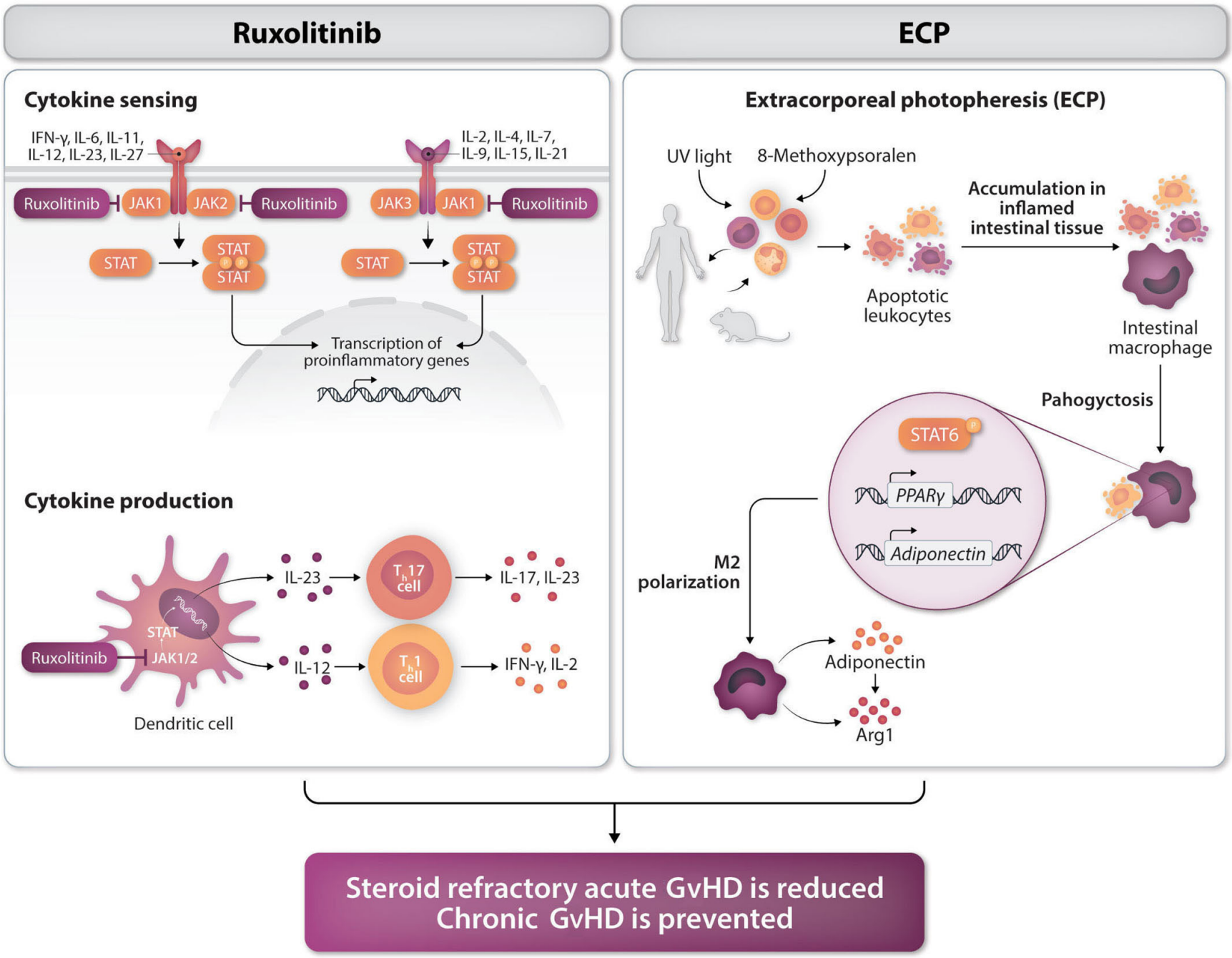

Figure 1. Proposed mechanism of action of ruxolitinib and extracorporeal photopheresis for acute steroid-refractory graft-*versus*-host disease. Ruxolitinib inhibits downstream signaling of multiple cytokine receptors and growth factors. Extracorporeal photopheresis (ECP) induces apoptotic cells that are taken up by local macrophages and induce tolerance. GvHD: graft-*versus*-host disease; UV: ultraviolet.

not significant, more patients within the RUX/ECP arm deceased within one year after experiencing aGvHD, mainly for infectious complications in the study by Lastovytska *et al*. Safety of the combination treatment with ruxolitinib and ECP should be analyzed in detail in the prospective setting. Taken together, the results of the study by Lastovytska *et al*. combining ruxolitinib and ECP as second-line treatment for aGvHD after allo-HSCT are promising. However, several factors, such as imbalanced aGvHD grades among the two cohorts, the historical control group, longer ruxolitinib treatment duration in the RUX-ECP arm, higher death rates in the RUX-ECP treated patients, and other, unknown, variables might have biased the outcome. Randomized prospective studies should be performed to confirm these findings.

Disclosures

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Contributions

All authors reviewed the literature, wrote the manuscript, and designed the figure.

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