Mesenchymal stromal cells to induce tolerance to solid organ transplantation

CHAPTER 10

VALORISATION OF THE RESEARCH

Improvement of current treatment outcome in transplant recipients of solid organs

Outcomes for solid organ transplantation have improved significantly during the last two decades. Improved immunosuppressive regimens have drastically reduced acute rejection rate. Among the renal transplants performed in Europe since 2000, overall patient and graft survival were 96% and 89% at 1 year, respectively. However, reduced acute rejection rate has not been automatically followed by better long term graft survival. In the United States on a total of 252,910 patients receiving a single organ kidney transplant between 1989 and 2009, graft half-life for deceased-donor transplant was 6.6 years in 1989 and increased to 8.8 by 2005. In low-risk populations like living-donor-recipients half life did not change, with 11.4 years in 1989 and 11.9 years in 2005. Thus, long term graft survival had in fact changed very little despite dramatic short term improvement. Especially now, when first year survival rates are most close to perfect, it becomes clear that further improvements in long term survival are the goals on which transplant community has to shift its attention. Chronic rejection and complications of immunosuppressive therapy significantly affected long term graft survival, keeping long term graft loss a constant phenomenon. The very same medications that have allowed for short term survival improvement have specific side effects while additively contributing to an overall state of immunosuppression and to the increased risk of cardiovascular disease. Most immunosuppressive regimens are currently based on the combination of calcineurin inhibitor with anti-proliferative agents and steroids and associated with new-onset diabetes mellitus, hypertension, hyperlipidemia and polyoma virus-associated nephropathy, and for calcineurin inhibitors also nephrotoxicity. Cardiovascular disease mainly accounts for deaths with functioning graft and is responsible for deaths in kidney transplant recipients beyond the first post-transplant year. Infections are responsible for 11.7 % of deaths and there is abundant evidence that cancer is increased in kidney transplant recipients because of immunosuppressive agents. Compared with the general population, mortality in transplant recipients is 4 times higher after the first year post-transplant. Nevertheless, in relation to acceptance of the allograft, immunosuppressants are indispensable in the clinical setting, as withdrawal of immunosuppressive therapy typically results in rejection of the transplanted organ.

Ideally, the induction of donor-specific tolerance would overcome these shortcomings, possibly allowing indefinite graft survival. Cellular therapy with immunological active cells is an intriguing new idea that has recently emerged to induce specific graft acceptance, and MSC are considered one of the most promising candidates. MSC may promote a pro-tolerogenic immune environment in transplant patients which could allow minimization or even discontinuation of immunosuppressive drugs in the long term, limiting the high risk of morbidity and mortality currently seen in solid organ transplant recipients related to drug-induced infections, malignancies and cardiovascular

diseases. Maintaining the health of transplanted organs not only protects the recipients of transplants from death, re-transplantation, or other trauma; it also protects the scarce availability of organs.

Impact on clinical management and transplant patients well being

Chronic immunosuppressive treatments have been linked to physical complications that, although not life-threatening, greatly impact on post-transplant quality of life. Immunosuppression-related physical effects that can alter appearance - including hirsutism, gingival hyperplasia, weight gain, cushingoid faces, hand tremors, alopecia and skin disorders - are among the most bothersome to patients and may have serious psychosocial implications, including sexual dysfunction. The myriad of side effects associated with immunosuppression include also osteoporosis, mood disorders, headaches, insomnia, paresthesias, gastrointestinal disorders (dyspepsia, gastritis, peptic ulcer disease and diarrhoea, constipation, nausea, vomiting, and anorexia) and skin disorders (skin thinning, purpura, acne, condyloma acumination and skin cancer). Pregnancy in transplanted women is considered high risk. These women also may have other co-morbidities, such as hypertension and diabetes mellitus which put them in an even higher risk category. These include high risk for spontaneous abortions, intrauterine growth retardation, preeclampsia and worsening of pre-existing hypertension, premature delivery, less-than-normal gestational weight and acute kidney graft rejection. All these side effects greatly impact on quality of life and have serious psychosocial implications. Moreover, on the long term these side effects could lead patients to non-compliance to immunosuppressive therapy. Indeed, in recent years, non-adherence to medication regimens has emerged as a major risk factor for acute rejection and graft loss. Despite these serious consequences non compliance is frequent among transplant recipients. Transplant recipients are required to manage a strict regimen of multiple medications changes in dosage schedules and medication physical side effects and it is estimated that up to 67% of patients do not take immunosuppressive medications as prescribed.

Therefore, MSC-based cellular therapy in solid organ transplantation, able to reduce or even eliminate the need of chronic administration of immunosuppressive drugs is likely to allow better clinical management of transplanted patients and eventually have a major impact on their quality of life.

Impact on health economy

The cost of maintenance immunosuppressive drugs is very high and is estimated around 15,000 Euro per year/patient. Moreover, because immunosuppressive therapy is complex, patients must be

monitored for both drug effectiveness and side effects by an experienced physician. Informal estimates suggest that the ambulatory visits and laboratory work solely to monitor immunosuppressive drugs could cost each patient roughly 1500 Euro per year. Further costs derive from additional outpatient medications such as antihypertensive agents and antibiotics for infections. Management of immunosuppressive drug side effects often requires additional medications and additional costs. Reducing the requirement of immunosuppressive drugs by using the MSC product to dampen immunological response to kidney and liver transplantation would result in reduction of overall costs for drug supply and management of solid organ transplant patients.

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