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INVITED COMMENTARY

The long and winding road towards induction of allograft tolerance in the clinic

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For all those among us who lived the history of immunosuppression in clinical transplantation over the last 25 years, the balance is certainly less optimistic than what we could have imagined.

The beginning of the 1980s, a time when only corticosteroids, azathioprine and anti-lymphocyte serum were available, represented the starting point of two fascinating decades affording the possibility to use in the clinic a wealth of chemical and biological immunosuppressants, which became more and more selective for defined subsets of immune cells, in particular T lymphocytes, and whose activities were targeted to intracellular processes.

However, these approaches were essentially based on immunosuppression which was non-specific, unrelated to the alloantigens involved. Furthermore, as drug association became the rule, we completely lost in clinical practice the benefit of the cell selectivity of the individual agents. Thus, we were left with very potent and broad immunosuppressive protocols, which were certainly effective at preventing acute rejection but not chronic rejection and which, in addition, exposed the patients to a higher risk of infections and tumors, as a consequence of over-immunosuppression. One must admit that these results completely disprove the long-held dogma that acute rejection was the main factor leading to chronic allograft dysfunction, the major justification for using very aggressive immunosuppressive protocols in the early post-transplant period.

Should not we step back, facing today's reality with humility and admitting that although major progress was made the situation is not ideal and that, at least in theory, inducing operational tolerance represents the only solution for this complex situation? The problem is, however, how to accomplish this change within an ethically acceptable frame for the well-being of our patients and considering that with conventional immunosuppressants we achieve about 95% survival one-year post-transplant with almost no acute rejection.

This is the topic addressed by the two companion papers from the group of F. Fandrich in this issue of Transplant International presenting results from clinical transfer of a novel cell therapy strategy [1,2].

Back in 2002, these authors described the tolerogenic capacity of a subset of monocytes, they named TAIC for 'transplant acceptance-inducing cells' that were initially characterized from the spleen and tested first in a heterotopic heart allograft model in the rat and subsequently in pig recipients of allogeneic lungs [3–5].

The first clinical study (TAIC-I) included recipients of a cadaver kidney transplant and essentially confirmed the feasibility of producing a sufficient number of TAICs under GMP conditions and indicated that the infusion of the cell preparations at the time of transplantation was

safe and did not promote any major side-effects [1]. Then, a more ambitious and meaningful study, TAIC-II, was performed, the design of which differed from TAIC-I in four main aspects: first, it included recipients of a living donor kidney; second, the cell inoculum included not only *in vitro*-cultured donor monocytes (as used in TAIC-I) but was in fact a mixture of TAICs and recipients' lymphocytes, which have been co-cultured for four days prior to infusion; third, the cell preparation was injected 5 days pre transplant to reproduce at best the protocol which gave the bests results in the experimental setting and fourth, the immunosuppressive regimen included ATG [2].

Although, for obvious reasons, no definitive conclusions may be drawn from trials including such a limited number of patients, the results appear quite remarkable in three respects. First, effective drug minimization was successfully achieved in four out of the five patients and in one patient normal graft function was maintained in total absence of immunosuppressants for 8 consecutive months. Second, in three of the recipients *in vitro* tests showed an undetectable anti-donor T-cell response with conserved third party responses at time points of follow up, where normal graft function was observed during drug minimization and also in the one patient weaned from all immunosuppressants. Third, none of the recipients developed an anti-donor humoral response, which so far represented a major problem with protocols aiming at tolerance induction such as those recently reported using donor bone marrow infusion [6].

These results illustrate very well the problems these types of protocols pose that are linked to both practical and fundamental issues.

Listing salient features, one should highlight:

1. The absolute need, as with all new clinical therapeutic strategies, to have an adequate control group, which allows drawing firm conclusions. For instance in the present case, as the authors very well discuss, the lack of such a control makes it difficult to conclude on the TAIC inoculum being responsible for the effect observed.

2. The importance of the choice of the induction therapy used. Favoring the use of biological agents, at least during the first days post-transplant, appears sensible given all the available data in the literature showing their tolerogenic potential [7–13].

3. The importance of having validated immunologic tests to adequately monitor drug-tapering in these patients. The present results, which could be obtained through an effective collaboration between clinicians and immunologists gathering efforts in the context of a European consortium (RISET-FP7), well illustrate this point. One would have liked to see a closer monitoring of the patient in whom immunosuppressants were completely stopped for 8 months. In this patient, the last mixed lymphocyte culture was performed 16 weeks before he developed the rejection episode which demanded reinstituting tacrolimus treatment. It is crucial for the future tenability of this type of trials to know whether these types of tests may raise 'red flags' in order to prevent exposing patients to acute rejection.

4. So far, the experience is, in fact, that these strategies generate a higher rate of acute rejection. The question is then what is the limit we should not transgress in order not to endanger graft survival? The answer is linked to the previous comment and will probably be the very careful adaptation of monitoring strategies for immunologic, histologic parameters as well as methods to assess graft function.

To conclude, it is important to recall that recently there were very interesting clinical reports from protocols aiming at transplantation tolerance. They mostly used cell therapy approaches under the form of donor bone marrow or mesenchymal stem cells [6,14]. Interestingly, it appears that peripheral tolerance immune mechanisms are implicated, at least in part, in the therapeutic effect observed.

The field is moving slowly but surely. This is already a very important fact, which speaks by itself!

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