Transplant Immunology 19 (2008) 229–234

Contents lists available at ScienceDirect

Transplant Immunology

journal homepage: www.elsevier.com/locate/trim

Tapering immunosuppressive therapy significantly improves *in vivo* cutaneous delayed type hypersensitivity responses

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ARTICLE INFO

Article history:
Received 4 April 2008
Received in revised form 22 May 2008
Accepted 23 May 2008

Keywords:
Azathioprine
Delayed type hypersensitivity
Immunosuppression
Kidney transplantation
Mycophenolate mofetil

ABSTRACT

Immunosuppressive therapy affects cell-mediated immunity and thereby increases the frequency of infections and malignancies in transplanted patients. We questioned whether reducing the immunosuppressive dose in stable kidney transplant patients has an *in vivo* effect on cutaneous delayed type hypersensitivity responses (DTH) reflecting cell-mediated immunity.

We measured DTH responses to recall antigens (Tetanus, Diphteria, Streptococcus, Tuberculin, Candida, Trychophyton, Proteus, glycerin control) on the volar surface of the forearm in patients before and after successful reduction (50%) of the dose of mycophenolate mofetil (MMF) or azathioprine (AZA). In addition, we tested healthy individuals who were age- and sex-matched to the patient group. Results of the skin reaction test were calculated as the sum in millimeters (mm) of all positive reactions (score), and as the number of positive antigens.

Patients treated with a high dose of MMF or AZA had a significantly lower test score compared to healthy controls ($p=0.01$). Also the number of positive antigens was reduced in patients compared to healthy controls ($p=0.02$). After reduction of the MMF or AZA dose, the test score and the number of positive antigens increased significantly ($p=0.02$, $p=0.01$, respectively) to comparable scores of healthy controls. Additionally, the mycophenolic acid (MPA) trough level was negatively correlated with the test score ($p=0.006$) and number of positive antigens ($p=0.004$).

In conclusion, successful tapering of the MMF or AZA dose in kidney transplant patients more than 2 years after transplantation favorably affects the *in vivo* DTH response, reflecting an improvement of the general immunity, facilitating the defense against infection and malignancies.

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1. Introduction

The human immune system is composed of multiple interacting elements including contributions from both humoral and cell-mediated arms. These elements play unique roles and interact in various ways with each other in maintaining the optimum immune status and health of humans. Cell-mediated immunity (CMI) involving sensitized T-lymphocytes is important in defense against certain infectious agents (e.g. viruses and fungi), in surveillance against neoplastic cells, and in regulation of immune function. Immunosuppressive therapy tends to reduce these mechanisms and thereby increases the frequency of recurring infections or malignancies in transplanted patients.

CMI function testing has traditionally been done by skin testing with cutaneous placement of recall antigens (delayed type hypersensitivity: DTH). By introducing an antigen to which an individual has been previously exposed, the capacity of T-lymphocytes to respond to an antigen in memory can be assessed. DTH response to recall antigens implies the presence of antigen-specific memory T cells, antigen presentation, and the recruitment of inflammatory cells as T-lymphocytes and monocytes [1].

Measurement of cutaneous DTH responses to a battery of commonly encountered antigens is a generally accepted and preferred means of assessing CMI function. In the past, such DTH testing suffered from lack of standardization of testing techniques, number and characterization of reactions, doses employed and interpretation of reactions and results. A commercially available system (Multitest® CMI device; Pasteur Mérieux Serums and Vaccines, SA, Lyon, France) has solved these problems by providing simultaneous and reproducible application of seven standardized recall antigens as a means of measuring DTH in assessment of CMI [2–6]. Because of its properties, widespread clinical acceptance, ease of use, and availability of scientific studies from other investigators, this system was adopted for the present study.

Immunosuppression could influence the DTH response in patients. While CsA monotherapy after kidney transplantation [7] and dermatological disorders [8,9] has no effect on cutaneous DTH responses to recall

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doi:10.1016/j.trim.2008.05.008

Table 1
Characteristics of kidney transplant recipients who were tapered in their mycophenolate mofetil (MMF) or azathioprine (AZA) dose

Patient	LR/LU[a] or PM[b]	Male/ female	Time after KTx[c] (in years)	Immunosuppression before tapering		Immunosuppression after tapering	
				MMF or AZA (mg/d)	Pred (mg/d)	MMF or AZA (mg/d)	Pred (mg/d)
1	LR	M	3.64	2000 MMF	10	[d]	
2	LR	M	6.13	100 AZA	7.5	75 AZA	7.5
3	LR	M	7.30	150 AZA	10	50 AZA	10
4	PM	F	6.16	100 AZA	10	50 AZA	10
5	LR	M	3.53	2000 MMF	10	1000 MMF	10
6	LR	M	4.72	2000 MMF	10	1000 MMF	10
7	LR	M	6.06	200 AZA	10	100 AZA	10
8	LR	M	6.94	175 AZA	10	75 AZA	10
9	LR	F	3.05	2000 MMF	10	1000 MMF	10
10	LU	F	3.89	2000 MMF	10	1000 MMF	10
11	LR	F	9.18	100 AZA	7.5	[f]	
12	LR	M	3.95	2000 MMF	7.5	1000 MMF	7.5
13	LU	M	2.99	2000 MMF	10	[e]	
14	PM	M	3.87	2000 MMF	10	[g]	
15	LR	M	6.08	2000 MMF	10	[f]	
16	LR	F	9.28	100 AZA	10	75 AZA	7.5
17	LR	M	3.05	2000 MMF	10	[g]	
18	LU	F	2.36	2000 MMF	10	1000 MMF	10
19	PM	M	3.72	2000 MMF	10	1000 MMF	10
20	LU	M	3.16	2000 MMF	10	1000 MMF	10
21	LR	M	3.58	2000 MMF	10	[f]	
22	LR	M	6.98	2000 MMF	10	1000 MMF	10
23	LR	M	11.01	100 AZA	10	50 AZA	10

[a] LR/LU: kidney donation from a living-(un)related donor.
[b] PM: kidney donation from a deceased donor.
[c] KTx: kidney transplantation.
[d] Chronic allograft nephropathy.
[e] Glaucoma.
[f] Follow-up in another clinic.
[g] Not reduced in their immunosuppressive medication (personal feeling).

antigens, these responses are impaired in kidney transplant recipients treated with azathioprine (AZA) and prednisone, CsA and prednisolone, or CsA and mycophenolate mofetil (MMF) and prednisolone compared to healthy individuals [10,11]. MMF also decreased the DTH response in patients with rheumatoid arthritis [12].

With the use of increasingly more potent immunosuppressive agents the rates of acute rejection at 6 months after deceased donor kidney transplantation have declined to 9–13% nowadays with a 5 years graft survival of 70–75% in patients treated with calcineurine inhibitors (CNI) and MMF [13]. The risks of infections and virus-induced malignancies are largely related to the total burden of immunosuppression [14,15]. Consequently, optimal immunosuppression, in which a balance is maintained between prevention of rejection and avoidance of infections, is the most challenging aspect of posttransplantation care. The long-term goal for optimal care of transplant recipients, with respect to infection, is the prevention and/or early recognition and treatment of infections while avoiding drug-related toxicities and malignancies.

In our transplant center, patients were converted from CNI to less toxic agent MMF or AZA [16,17] to avoid CNI related adverse events [18–20] and to improve the long-term graft and patient survival. After discontinuation of CNI, the immunosuppression was further reduced to approximately 50% MMF or AZA [21,22] to minimize side effects of immunosuppression. Recently, we demonstrated that tapering of AZA or MMF dose decreases the precursor frequency of donor-reactive cytotoxic T-lymphocytes, while the donor-reactive T cell proliferation and cytokine production capacity remained unchanged [22].

2. Objective

The delayed hypersensitivity skin test reactivity is a sensitive, easy and reproducible method as a reflection of memory response to recall

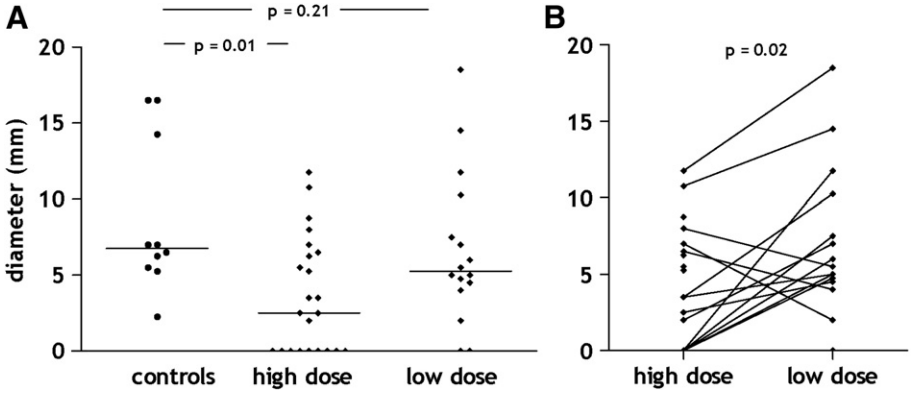

Fig. 1. (A) Average diameters of cutaneous delayed type hypersensitivity (DTH) test in healthy controls and in patients with high or low dose immunosuppressive medication. (B) Paired data from patients with high or low dose immunosuppressive medication.

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