Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Evolution of immunoglobulin and mannose binding protein levels after renal transplantation: association with infectious complications

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Keywords
Immunoglobulins, infections, mannose binding protein, renal transplantation.

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Received: 16 May 2007
Revision requested: 3 July 2007
Accepted: 17 August 2007

doi:10.1111/j.1432-2277.2007.00556.x

Summary

Hypogammaglobulinemia (hypo-Ig) and low mannose binding protein (MBP) levels might be involved in the infectious risk in renal transplantation. In 152 kidney transplant recipients treated with calcineurin inhibitors (CNI) and mycophenolate mofetil (MMF), during the first year, we prospectively recorded the incidence of hypogammaglobulinemia, and low MBP levels. Their influence on infectious complications was evaluated in 92 patients at 3 and 12 months (T3 and T12). The proportion of deficiency increased significantly: hypo-IgG: 6% (T0), 45% (T3), and 30% (T12) ($P < 0.001$); hypo-MBP: 5%, 11%, and 12% ($P = 0.035$). Hypo-IgG at T3 was not associated with an increased incidence of first-year infections. A significantly higher proportion of patients with combined hypogammaglobulinemia [IgG+ (IgA and/or IgM)] at T3 and with isolated hypo-IgG at T0 developed infections until T3 compared with patients free of these deficits ($P < 0.05$). Low MBP levels at T3 were associated with more sepsis and viral infections. Hypogammaglobulinemia is frequent during the first year after renal transplantation in patients treated with a CNI and MMF. Hypo-IgG at T0 and combined Igs defects at T3 were associated with more infections. MBP deficiency might emerge as an important determinant of the post-transplant infectious risk.

Introduction

Infectious diseases remain a major cause of morbidity and mortality in allograft recipients. Besides defects in T-cell responses, the impairment of antibody synthesis has been identified as a major pathogenic factor. Indeed, hypogammaglobulinemia is a well-known side effect of immunosuppressive therapy in solid organ transplant recipients [1–7] and has been repeatedly associated with infectious episodes [1–3,5,6,8]. The proportion of patients who develop post-transplant hypogammaglobulinemia varies according to both the type of solid organ transplanted and the nature of the immunosuppressive regimen. Only scarce data are available on this topic in renal transplantation. Low IgG levels were found to be present in 26% of patients treated with azathioprine (AZA) and ciclosporin A (CsA) when evaluated at a mean of 6 years after transplantation [6]. With regard to the widely used combination of a calcineurin inhibitor (CNI) and mycophenolate mofetil (MMF), a single small series of 24 renal transplant patients had a 46% incidence of hypo-IgG during the first 6 post-transplant months [7]. Data from heart transplant recipients have shown that the number of circulating B cells were lower among patients treated by MMF compared with that among patients given

[Corrections added after online publication 8th October 2007: Errors to author names Marc Hazzan, Françoise Mascart and Anh-Dung Hoang were corrected along with the first letter of hypogammaglobulinemia being capitalised in line 14 of the Summary].

azathioprine [9]. From a functional point of view, the antibody responses to vaccines or xenogeneic proteins such as ATGAM or OKT3 were lower among MMF-treated patients than among AZA-treated patients [10–14]. Thus, more data on immunoglobulin levels during the first post-transplant year among renal transplant recipients treated with the association of CNI and MMF and their possible association with infectious episodes are needed.

In addition to immunoglobulins, mannose binding protein (MBP), a lectin of hepatic origin, may be of importance in first-line, innate immune response against both bacterial and viral pathogens. MBP can bind carbohydrates expressed on the surfaces of pathogens through its lectin domain. Once bound to its ligands, MBP is able to activate complement in an antibody-and C1q-independent manner, and to opsonize bound bacteria using the C1q-receptor on macrophages [15]. The MBP gene is subject to several mutations resulting in reduced MBP levels and functional deficiency. The frequency of heterozygote and the frequency of homozygote mutations are about 33% and 5% respectively in most populations. Plasma concentrations are about 20% lower in heterozygotes, and are nearly absent (<2% of normal levels) in homozygotes [16]. MBP deficiencies have been associated with infections in several clinical settings such as an enhanced susceptibility to infections in children [17], a lower survival for MBP mutation carriers among patients with cystic fibrosis [18], and an increased incidence of major infections after allogeneic hemopoietic stem cell transplantation [19]. Recently, an association was found between MBP deficiency and cytomegalovirus infection after kidney transplantation in a small series of patients. [20]. According to several studies, a level of MBP < 1 μg/ml confers an increased risk of infection [21]. To date, the influence of immunosuppressive therapy on MBP serum levels and the possible association between low MBP levels and infectious episodes have not been evaluated in solid organ transplant recipients.

The aim of this study was to evaluate the kinetics of serum levels of IgG, IgA, IgM, and those of MBP in patients treated with MMF and a CNI during the first year of renal transplantation. In addition, we investigated the association of these deficits with infectious complications.

Methods

Patients and controls

One hundred and eighty-one adult transplant recipients who received a single renal graft between January 1999 and August 2002 were screened on the day of transplantation and considered for the study. One hundred and fifty-two were alive with a functional graft at 1 year, and had all the required samples available for analysis. They form the basis of the report. The patients were transplanted in two centers: Hospital Erasme in Brussels, Belgium, ($n = 94$) and Hospital Calmette in Lille, France ($n = 58$). Their main demographic characteristics were: gender: 60.5% males; mean age: 45.2 ± 13.2 years; 140 were recipients of their first renal allograft, nine of their second, and three of their third graft. Anti HLA antibodies were ≤5% in 128 patients, between 6 and 79% in 17 patients, and >80% in seven. With regard to immunosuppressive therapy in Brussels, all patients ($n = 94$) received a calcineurin inhibitor as main immunosuppressive drug [tacrolimus (TRL), $n = 78$; CsA, $n = 16$] together with MMF and steroids. The proportion of patients free of steroids was 0% at 3 months, 13% at 6 months, 23% at 9 months, and 28% at 12 months. The mean doses of prednisolone in patients on steroids were (mg/kg/day ± SD): month 1: 0.2 ± 0.05, month 3: 0.12 ± 0.03, month 6: 0.09 ± 0.06, month 12: 0.08 ± 0.06. In addition, induction therapy was given to 77 patients (82%): anti-IL2 receptor monoclonal antibodies, N = 43; ATG, N = 19; and OKT3, N = 15. In Lille ($n = 58$), all patients received the same immunosuppressive therapy for 3 months: ATG + CsA + MMF + steroids. After 3 months, they were randomized to receive either MMF + steroids ($n = 28$) or CsA + steroids ($n = 30$). All patients were followed up for 1 year.

Study procedure

Serum samples were collected just before transplantation (T0), at 3 and 12 months (T3 and T12), and were stored at −20 °C until analysis. Immunoglobulins (IgG, IgA, IgM) and mannose binding protein (MBP) levels were measured by nephelometry with the analyzer 'Behring II' system in the 152 patients at T0, T3 and T12. Results were expressed in mg/dl for Igs (Normal values: IgG: 650–1500; IgA: 75–400; IgM: 40–250) and in μg/ml for MBP (Nl: 1–5); hypo-MBP is considered for values <1 μg/ml) [16].

Infectious episodes

The occurrence of infections and other clinical and biological data of all kidney transplant recipients are routinely and prospectively collected and recorded in a computer database at the Erasme Hospital. These data were used to investigate the possible associations between immune deficiency states and the occurrence of infectious episodes during the first post-transplant year in 92 out of the 94 patients (the serum was not available at 3 months in two patients) transplanted in the Erasme Hospital in Brussels. The cumulative incidence of infections at T3 and T12 was then calculated for statistical analysis. Infections were recorded, if they were treated with either anti-

biotics or antiviral therapy, or were due to BK polyomavirus. The infections that occurred in our patient population were: (i) urinary tract infections, defined by positive cultures with more than 100 000 colonies/ml; (ii) respiratory infections (bronchitis or pneumonia) diagnosed by clinical observation, pathogen identification, and chest–X-ray; (iii) viral infection, either due to: (a) cytomegalovirus (CMV), diagnosed by either antigenemia or polymerase chain reaction (PCR). Of note, all the patients received CMV prophylaxis for 3 months (either acyclovir for CMV seropositive recipients, or ganciclovir in case of seronegative reipients of a CMV seropositive kidney donor); (b) BK polyomavirus, diagnosed by a positive PCR in urine and histological findings of BKV nephritis; (c) Herpes zoster virus (HZV) diagnosed by clinical observation; (iv) sepsis according to positive hemocultures. There were no cases in this present series of abdominal infection, wound infections, etc. To investigate the possible associations between infectious episodes and deficits in immunoglobulins or MBP, patients were categorized as either deficient or normal according to their values of IgG, IgA, IgM and MBP levels at 3 months as defined above. The primary outcome of these analysis was the comparison of the proportion of patients with ≥1 infection(s) for the periods between T0 and T3, as well as between T4 and T12.

Statistical analysis

Categorical data are presented as proportions and hypothesis testing was performed by the bilateral Fischer's exact test. Continuous data for antibody titers are presented as means ± SEM (IgG, IgA, IgM, MBP). Hypothesis testing for differences between patient categories was performed with the Mann–Whitney test. Hypothesis testing for paired data was performed with the Wilcoxon signed rank test. Hypothesis testing for repeated measures was performed by repeated-measures analysis of variance (ANOVA) for normally distributed data and the Friedmann test for data that were not normally distributed. The effect of the type of induction therapy on the evolution of immunoglobulin and MBP levels during the first year was assessed by adding the type of induction therapy as a inter-subject variability factor into the ANOVA model. The association at 3 months between trough levels of calcineurin inhibitors and immunoglobulin and MBP levels was investigated by visual inspection of the scatter plots and calculation of the Spearman correlation coefficient. Whether the relative risk of infectious complications associated with Ig deficits was modified by potential confounders and effect modifiers was tested by multivariate logistic regression modeling. For rare outcomes that did not allow multivariate modeling, the effect of potential confounders and effect modifiers was tested by stratification and calculation of the adjusted odds ratio. The following variables were tested as potential confounders and effect modifiers: age, gender, diabetes (either pre- or post-transplant), hepatitis C carriage, number of transplantation, time on dialysis, renal function, splenectomy, Ab induction therapy, use of tacrolimus versus CsA, treated rejection episodes. A probability value of the null hypothesis of $P < 0.05$ was considered statistically significant.

Results

Immunoglobulin G (IgG)

In the whole cohort (N = 152), the mean levels (±SEM) of IgG decreased from 1143 ± 31 mg/dl (T0) to 713 ± 21 (T3) and rose to 852 ± 24 at T12 ($P < 0.001$) (Fig. 1). The incidence of hypo-IgG (<650 mg/dl) rose from 6% at T0 to 45% at T3 and 30% at T12 ($P < 0.001$) (Fig. 2).

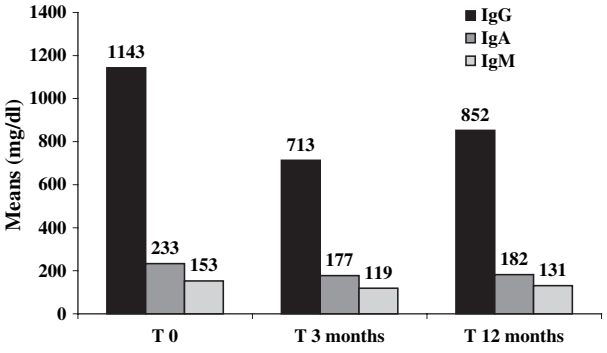

Figure 1 Immunoglobulin levels during the first year after renal transplantation The mean levels are indicated on top of columns. $P < 0.001$, by anova for repeated measures, for IgG, IgA, and IgM when T0, T3, and T12 are compared.

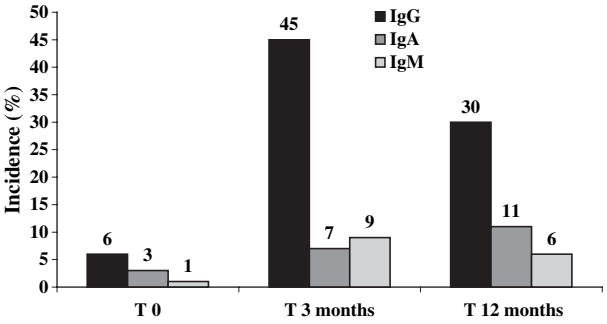

Figure 2 Incidence of hypogammaglobulinemia during the first year after renal transplantation The proportions are indicated on top of columns. When the different times are compared, $P < 0.001$ for IgG, $P = 0.027$ for IgA, and $P = 0.018$ for IgM.

Table 1. Immunoglobulins deficits at 1 year among patients receiving either ciclosporin A (CsA) or mycophenolate mofetil (MMF).

% of patients with	CsA-Pds (N = 30)	MMF-Pds (N = 28)	*P*
Hypo-IgG	43%	50%	NS
Hypo-IgA	7%	33%	0.034
Hypo-IgM	3%	17%	0.11
Mean serum levels (mg/dl ± SEM)			
IgG	731 ± 43	691 ± 34	0.28
IgA	163 ± 14	142 ± 12	NS
IgM	148 ± 14	86 ± 7	<0.001

Patients under CsA + MMF + steroids were randomized at 3 months to receive either CsA + steroids or MMF + steroids. Results were analyzed at 12 months.

We separately analyzed the 58 patients who were randomized at 3 months to receive either MMF-steroids (N = 28) or CsA-steroids (N = 30) double therapy for the rest of the first year after transplantation. We found no difference either in the incidence of hypo-IgG at T12 (MMF-steroids, 50%; CsA-steroids, 43%) or in the mean IgG levels (Table 1).

Immunoglobulin A (IgA)

In the whole cohort (N = 152), the mean levels (±SEM) of IgA decreased from 233 ± 7 mg/dl (T0) to 177 ± 6 (T3) and rose to 182 ± 7 at T12 ($P < 0.001$) (Fig. 1). The incidence of hypo-IgA (<75 mg/dl) rose from 3% at T0 to 7% at T3 and 11% at T12 ($P = 0.027$) (Fig. 2). At T12, the incidence of hypo-IgA was numerically but not statistically higher among patients randomized at 3 months to receive MMF-steroids than among patients who received CsA-steroids (25% vs. 7%, $P = 0.075$). However, blood levels were not different between the two groups (Table 1).

Immunoglobulin M (IgM)

In the whole cohort (N = 152), the mean levels (±SEM) of IgM decreased from 153 ± 7 mg/dl (T0) to 119 ± 5 (T3) and rose to 131 ± 7 at T12 ($P < 0.001$) (Fig. 1). The incidence of hypo-IgM (<40 mg/dl) rose from 1% at T0 to 9% at T3 and 6% at T12 ($P = 0.018$) (Fig. 2). A sub-analysis of the 58 patients randomized to receive either MMF-steroids or CsA-steroids showed a trend to a higher incidence of hypo-IgM at T12 among patients receiving MMF (14% vs. 3%, $P = 0.19$). Furthermore, at T12, IgM levels were significantly lower under MMF-steroid therapy compared with CsA-steroids (86 ± 7 vs. 148 ± 14mg/dl, $P < 0.001$) (Table 1).

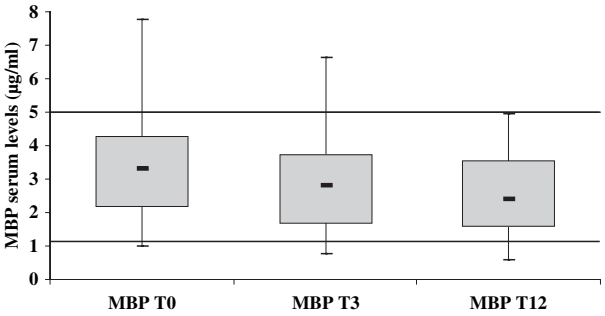

Figure 3 Mannose binding protein levels during the first year after renal transplantation The normal MBP values fall within the 2 horizontal lines (1–5 µg/ml). The short line within the box represents the median of the given variable. The bottom and top edges represent the 25th and 75th percentiles. In other words, 50% of the data fall within the box, and 5% each above and below. The 'whiskers' extend to the 5th and 95th percentiles. $P < 0.001$, ANOVA repeated measures.

Combined Igs deficiencies

At 3 months, 10/150 patients (7%) had combined hypo-IgG and hypo-IgA levels; 10/151 patients (7%) had combined hypo-IgG and hypo-IgM levels; and 3/150 (2%) had a pan-hypogammaglobulinemia.

Mannose-binding-protein

The mean levels (±SEM) of MBP decreased from 3.6 ± 0.2 µg/ml (T0) to 3.0 ± 0.1 (T3) and 2.7 ± 0.1 (T12) ($P < 0.001$) (Fig. 3). The incidence of hypo-MBP rose from 5% at T0 to 11% at T3 ($P = 0.08$) and 12% at T12 ($P = 0.035$ vs. T0). At T12, there was no difference either in MBP levels or in the incidence of hypo-MBP between patients randomized to receive either MMF or CsA at 3 months (data not shown).

Associations between immunosuppressive therapy and deficits in immunoglobulins or MBP

As our patient cohort received different types of induction therapy (ATG, anti-IL2R mAb or no induction) and displayed variable blood trough levels of calcineurin inhibitors, it was important to search for possible associations between induction therapy as well as CNI exposure, and deficits in immunoglobulins or MBP.

First, we did not observe an association between the type of induction therapy and the decrease in serum levels of the different types of immunoglobulins or MBP during the first year after transplantation (for IgG, $P = 0.24$; for IgA, $P = 0.44$; for IgM, $P = 0.34$; for MBP, $P = 0.4$).

Second, we investigated the possible association between calcineurin inhibitor trough levels at 3 months

Table 2. Cumulative incidence and nature of infectious episodes*.

Infections	At 3 months	At 12 months
All infections	47%	74%
Urinary tract infection	35%	53%
Respiratory tract infection	7%	27%
Viral infection	2%	9%†
Sepsis	0%	4%

Four out six patients who developed CMV disease were CMV seronegative recipients of seropositive kidney donnors (D+ R–) and two out of six presented a hypo-MBP at 3 months. One out of two patients who developed BK polyomavirus presented a hypo-MBP at 3 months.

*The proportion of patients with ≥1 infectious episode is shown at 3 and 12 months for the 92 patients grafted in Brussels.

†6% CMV; 2% BK polyomavirus, 1% HZV.

and immunoglobulin as well as MBP levels at the same time point. Trough levels were only available for patients transplanted at the Brussels centre. We found no association at 3 months between tacrolimus (N = 78) trough levels (range: 8 to 17 ng/ml; median: 12 ng/ml) and immunoglobulin G, A, or M or MBP levels. The number of patients treated with cyclosporine (N = 16) was too low for meaningful analyses.

Associations between infectious episodes and deficits in immunoglobulins or MBP

The cumulative incidence and the nature of infectious episodes that occurred during the first post-transplant year among 92 patients followed in Brussels are shown in Table 2. As commonly observed in other series, urinary tract infections were the most frequent events.

In case of isolated hypo-IgG at T3 (N = 33), we observed no increase in infectious complications either from T0 to T3 or from T4 to T12 (Table 3).

There were five patients with hypo-IgA and seven patients with hypo-IgM at T3. Most of these patients had combined Ig deficits. Indeed, two patients had a combined hypo-IgA + hypo-IgG, three had hypo-IgM and hypo-IgG, and two had deficits of IgG, IgA and IgM levels. Taken together, these seven patients with combined Ig deficits at T3 experienced more infectious events during the first 3 months (86% vs. 44% in patients without combined Ig deficits, risk ratio: 2 (95% CI 1.3–2.9), $P = 0.048$) (Table 3). The mean number of infectious episodes was 1.3, vs. 0.7 in patients without combined Ig deficits, $P = 0.02$. The increased risk was mainly because of an increased proportion of patients who developed respiratory infections during the first 3 months (43% vs. 5% in patients without combined Ig deficits, risk ratio 9.3 (95% CI 2.6–33.7), $P = 0.008$) (Table 3). Stratification for potential confounding variables did not modify the strength of the association between combined Ig deficits and the development of one or more infections during the first 3 months after transplantation (data not shown).

Although the association between T0 IgG levels and infections was not our primary outcome measure, we observed that five out of six patients with hypo-IgG at T0 developed at least one infection from T0 to T3. The mean number of infectious episodes per patient during the first 3 months was 1.5 (vs. 0.65 in patients with normal IgG levels at T0, $P = 0.012$). Both urinary and respiratory tract infections contributed to the increased incidence and number of infections in this patient category.

Table 3. Risk factors for infectious episodes.

	% of patients with ≥1 infection					
Déficiency at T3	T0 to T3			T4 to T12		
IgG	Low ($n = 33$)	Nl ($n = 59$)	*P*	Low ($n = 33$)	Nl ($n = 59$)	*P*
≥1 infection	51%	44%	NS	70%	54%	0.15
Urinary infections	36%	36%	NS	45%	32%	NS
Respiratory infections	15%	3%	0.09	21%	22%	NS
Combined Igs*	Low ($n = 7$)	Nl ($n = 85$)	*P*	Low ($n = 7$)	Nl ($n = 85$)	*P*
≥1 infection	86%	44%	0.048†	43%	61%	NS
Urinary infections	57%	34%	NS	29%	38%	NS
Respiratory infections	43%	5%	0.0085‡	14%	22%	NS
MBP	Low ($n = 11$)	Nl ($n = 81$)	*P*	Low ($n = 11$)	Nl ($n = 81$)	*P*
≥1 infection	27%	49%	NS	73%	58%	NS
Urinary infections	18%	38%	NS	45%	36%	NS
Respiratory infections	9%	7%	NS	36%	20%	NS

*Hypo-IgG associated with either hypo-IgA and/or hypo-IgM.

†By logistic regression analysis: O.R. 6.1, $P < 0.05$.

‡Logistic regression was not applicable because the number of events was too low. However, individual adjustments for covariates showed that none acted as a confounder or effect modifier.

With regard to deficiencies in MBP, hypo-MBP at T3 (N = 11) was not associated with an increased incidence of common infections (Table 3). However, although the numbers are small and must thus be taken with caution, we observed more episodes of sepsis among MBP-deficient patients. Indeed, two out of four septic episodes occurred in MBP-deficient patients (2/11 vs. 2/81 among patients free of hypo-MBP; number of episodes: 0.18 vs. 0.024, $P = 0.017$). Along the same line, the proportion of patients with hypo-MBP who developed viral infections was higher than patients with normal MBP levels (27% vs. 6%, risk ratio 4.4 (95% CI: 1.2–16, $P = 0.05$); number of episodes: 0.45 vs. 0.12, $P = 0.022$).

Discussion

The first finding of our study is the high incidence of hypogammaglobulinemia during the first year of transplantation. Indeed, hypo-IgG developed in nearly one-half (45%) of our renal transplant recipients at 3 months and was still highly prevalent at the end of the first year. This incidence is similar to that found by Keven [7], in a study where 49 renal transplant recipients were randomized to receive either MMF ($n = 24$) or AZA ($n = 17$). At 6 months, 46% of patients under MMF had hypo-IgG levels, while this occurred in only 12% of patients under AZA therapy. Other data also suggest that AZA is less prone to induce hypo-IgG than MMF, as indicated by a 26% incidence of hypo-IgG among renal transplant patients treated by CsA + AZA at a mean of 6 years after transplantation [3]. Hypo-IgG developed more frequently after lung transplantation in patients under MMF compared with patients under AZA [22]. In one series of heart transplant recipients under MMF therapy, hypo-IgG was mainly found after treatment of acute rejection with iv steroids [6]. Accordingly, five out of eight patients from our series treated with steroids pulses for rejection also developed hypo-IgG.

In addition to hypo-IgG, a sizeable fraction of our patients developed hypo-IgA and hypo-IgM at 3 and 12 months post-transplant. In a previously reported cohort, combined Ig deficits were found in approximately 10% of renal transplant recipients treated with CsA and AZA at a mean of 6 years post-transplant [3]. In a series of lung transplant recipients with hypo-IgG who were treated primarily with CsA and AZA, 26% also developed hypo-IgA and 9% hypo-IgM [2].

Among patients who were randomized at 3 months to receive either CsA + steroids or MMF + steroids, IgG and IgA levels were not different between the two groups at 1 year, but IgM levels were lower in the MMF group. Therefore, in this particular series of patients, our results do not support the notion that MMF more profoundly affects immunoglobulin synthesis than CsA, although longer follow-up duration may be necessary to unravel such difference.

With regard to risk factors for infections in addition to hypogammaglobilinemia, we confirmed previous observations that female gender [23,24] and higher age [25] are independent risk factors for infectious episodes during the first year (data not shown). We did not observe a difference in infectious episodes between patients treated with tacrolimus or cyclosporine (data not shown). After adjustment for these potential risk factors of infection, hypogammaglobulinemia at transplantation remained a significant predictor of infectious episodes during the early post-transplant period but not for the entire first year.

On the contrary, in our cohort, hypo-IgG at 3 months, although frequent, was not a risk factor for infections during the first year. There are discordant reports in the literature with regard to the association between hypo-IgG and infections. Thus, 26% of liver transplant patients under CsA and AZA were found to have hypogammaglobulinemia during the first post-transplant year, but none of the infectious outcome examined was associated with hypogammaglobulinemia [26]. Likewise, *de novo* hypogammaglobulinemia was a frequent finding (49%) among lung transplant recipients treated by tacrolimus and AZA, but was not associated with an increased incidence of infections [22]. On the other hand, a cross-sectional retrospective study of renal transplant recipients treated with CsA and AZA at more than 6 years revealed that among those with hypo-IgG, the prevalence of infectious complications was 77% compared to 31% in patients with normal IgG levels ($P < 0.005$) [3]. More recently, Keven found that 6 months after renal transplantation, among the recipients ($n = 24$) who were treated with MMF and a CNI, urinary infections occurred only in those with low IgG levels (seven out of 11 patients) [7]. At a mean of 2 years after lung transplantation, 70% of patients treated with AZA and CsA developed hypogammaglobulinemia. In this cohort, there was a significant, stepwise association between lower IgG levels and infectious episodes (79% of hypo-IgG patients had 'any infection' compared to 40% of recipients with normal values, $P < 0.006$) [2]. Likewise, 6 months after heart transplantation, recipients with severe '*de novo*' hypo-IgG (<350 mg/dl) had a higher incidence of opportunistic infections than the other patients (odds ratio: 22.8, $P < 0.0001$) [6]. In addition, hypogammaglobulinemia has been frequently observed among long term transplanted patients who experienced opportunistic and/or severe infections [1,4,27,28]. It is likely that parameters such as the duration of immunosuppression [3], the type of graft, and the nature of maintenance immuno-

suppression, all influence the impact of hypo-IgG on the susceptibility to infections. In our cohort, the lack of association between hypo-IgG at 3 months and infections might also be because of the policy of discontinuation of steroids that took place during the first post-transplant year [29].

Unlike hypo-IgG at T3, we found that hypo-IgG at T0 and combined Ig deficiency at 3 months were associated with infections and in particular respiratory tract infections. Therefore, these patients might benefit from therapy with intravenous immunoglobulin preparations as prophylaxis, or in case of occurrence of an infectious event.

Deficit in mannose binding protein has been identified as a risk factor for severe infections in several settings such as bone marrow transplantation [19]. Here, we did explore, for the first time, in a systematic manner, the relation between this effector molecule of innate immunity and infections in renal transplant recipients. We found that the mean levels of MBP significantly decreased during the first year of renal transplantation, although the mechanism behind this observation remains unknown. Interestingly, low MBP levels at 3 months were associated with an increased risk of sepsis and viral infections during the first year, suggesting that the protecting effect of this molecule is of importance in immunosuppressed patients. Along the same line, low MBP levels have recently been reported in kidney transplant recipients as a risk factor for the development of CMV disease in the D+/R− setting [20].

In summary, patients treated with the association of a CNI, MMF, and steroids show decreased levels of Immunoglobulins and MBP in the course of the first post-transplant year. Although the isolated IgG deficit at 3 months was not an independent risk factor for infections in our cohort, the combined hypo-Immunoglobulinemias (G + A) or (G + M) were associated with more frequent infections, respiratory in particular. Low MBP levels were associated with viral infections and sepsis. Further studies should help to define better the interest of MBP monitoring after renal transplantation.

Acknowledgements

This study received financial support from the Nephrology Department of Erasme Hospital, Brussels, Belgium.

Authorship

NB: performed reseach, collected data, wrote the paper. KMW: analyzed data. MH: collected data. LG: collected data. AH: collected data. CN: collected data. FM: designed research. DA: designed research, wrote the paper.

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