**ABSTRACT**

IgA Nephropathy (IgAN) recurs in up to two thirds of cases of transplanted kidneys, sometimes as early as 3 months after transplantation and frequently years later. While short-term analyses suggested that this recurrence does not significantly impair the graft survival, longer follow-ups have detected an increased risk of graft function loss in patients with IgAN recurrence. Little is known about the clinical risk factors for recurrence. The Italian Ministry of Health funded the formation of a network of nephrologists aimed at investigating the frequency of IgAN recurrence, risk factors, effect on graft function and strategies to limit renal transplant loss.

A consortium of 9 Nephrology and Immunogenetics Centres collected retrospective data from 361 patients with biopsy-proven IgAN as a cause of end-stage renal failure. These patients (291 males) were in median 31 years old at diagnosis (interquartile range, IQ 24-41) and followed for a median follow-up of 20 years (IQ 16-25) from onset of the IgAN in the native kidney. Recurrence of IgAN was defined when renal biopsy of the graft showed IgAN in subjects with haematuria and proteinuria >0.5 g/day.

Among the patients investigated, 74 (20.5%) had biopsy-confirmed recurrent transplant IgAN after a median 46 months (IQ 15-79 months) after transplantation. The rate of recurrence was similar in both sexes. HLA genetic background was not found to have an effect. No difference in recurrence was detected in living related donors versus cadaveric donors. At COX regression analysis, medium time average proteinuria in the first 3 years after transplantation was highly predictive of IgAN recurrence and age at onset of the original IgAN and its duration shorter than one year before need for dialysis showed borderline levels of statistical significance. The presence of recurrence in the grafted kidney significantly affected the grafted kidney survival to serum creatinine levels of >2 mg/dl.

Looking at immunological and genetic risk factors for IgAN recurrence in a subgroup of 61 patients with IgAN in the native kidney, 30 of them having developed recurrence of IgAN in the grafted kidney, we observed that patients with polymorphisms of TNF-α and IL-10 which down-regulate the Th2 subset, experienced less recurrence of IgAN, while the effect of high levels of aberrantly glycosylated IgA1 played only a borderline role in the development of IgAN recurrence.
In conclusion, recurrence of IgAN is frequent, affecting more than one quarter of patients after post-transplant follow-up longer than 5 years. The development of IgAN in the grafted kidney is associated with faster decline of renal function. Genetic factors conditioning a prevalence of the Th2 subset seem to play a role in the recurrence, in association with high levels of aberrantly glycosylated IgA1. The development and persistence of proteinuria during the post-transplant follow-up is the most sensitive predictive index for IgAN recurrence.

Key-Words: Kidney transplantation, IgA nephropathy, recurrence, risk factors.

INTRODUCTION

Primary IgA Nephropathy (IgAN) is a common glomerulonephritis worldwide, accounting for 20-30% of renal biopsies in Southern Europe, Japan and Australia1. Long-term studies have demonstrated that the rate of progression has an extremely wide range, from 5 to 25% after 10 years and 25-50% at 20 years, and complete remission is reported as well in 5 to 30% of cases2 (Table I). The bias in defining the natural history of IgAN is the pre-selection of patients enrolled in different stages of their clinical course. Indeed, patients with asymptomatic urinary abnormalities can only enter the cohorts with biopsy policy less restrictive than others with renal biopsy performed only in cases of proteinuria or reduced renal function3. In addition, there is a great variety in the natural history of individual patients with IgAN ranging from asymptomatic forms detected at kidney donation only – as reported in 16% of healthy subject in Japan4 – to rapidly progressive nephritis5. The overall analysis shows that IgAN is a progressive renal disease in a relevant percentage of patients, and in two decades follow-up half the patients are likely to develop end-stage renal failure with need of dialysis. Most of them – 67% of cases according to the ERA-EDTA Registry – are quite young when entering dialysis, aged between 25 and 55 years (22% are less than 30 years old)5. Among patients having received a kidney graft, 5-20% had IgAN as original disease. In conclusion, the prevalence of transplanted patients who had IgAN as original disease is quite large in each centre. They are young adults with high life and health expectancy and deserve every effort the nephrology scientific community can make to improve their outcome.

After renal transplantation, 26% to 46% of the patients7,8 have a recurrence of IgAN in the grafted kidney, up to 58% when patients had protocol biopsies with immunofluorescence routinely performed9.
Recurrence can be detected as early as 3 months after transplantation or a decade later\textsuperscript{10}. While early short-term follow-up suggested good graft prognosis in spite of IgA mesangial deposits, follow-ups longer than 5 years reported increased risk of progressive renal function loss\textsuperscript{11,12}. It is true that it is often difficult to distinguish the relative contribution of graft dysfunction due to recurrent IgAN and chronic allograft nephropathy. Chronic graft dysfunction may result from chronic allograft rejection, but also from hypertension, dyslipidaemia, calcineurine-inhibitor nephrotoxicity\textsuperscript{13}, while on the other hand IgA mesangial deposits may be a chance finding, which does not lead to renal damage. However, in expert hands and using immunofluorescence and electron microscopy, the relative contribution of IgAN and chronic allograft nephropathy can be assessed, and it is generally thought that the presence of IgA deposits worsens the graft survival over long term follow-up, even though the effect of IgAN recurrence \textit{per se} is likely to be amplified by an independent chronic graft damage.

\section*{FREQUENCY OF RECURRENT IgAN IN GRAFTED KIDNEYS}

The detection of IgA mesangial deposits in a grafted kidney without any urinary abnormality as a chance finding after protocol biopsy is not considered a true recurrence, and only its association with a clinical picture of microscopic haematuria often with some degree of proteinuria allows a clear diagnosis of IgAN recurrence\textsuperscript{11,12,14}. It is likely that recurrence of mesangial deposits and development of renal damage due to IgAN need time to develop, and indeed the longer the length of the follow-up the higher the rate of recurrence of IgAN in the grafted kidney. Most reports detect recurrence when patient follow-up is longer than 5 years. Similarly, the longer the follow-up, the higher the rate of progressive renal dysfunction in patients with IgAN recurrence.

Recurrent IgAN is diagnosed in 26-46\% of transplanted patients following the detection of urine abnormalities and this frequency increases to up to 58\% of cases when protocol biopsies are performed. In most cases the urine abnormalities are limited to microscopic haematuria with or without proteinuria. Only rarely proteinuria increases up to the nephrotic range, and exceptionally the clinical course follows a rapidly progressive decline\textsuperscript{15}. The renal biopsy usually detects only proliferative changes, rarely with crescents formation. The immunofluorescence pattern is similar to that observed in native kidney IgAN.

\section*{Clinical features and course of recurrent IgAN in grafted kidneys}

The Italian Ministry of Health funded the formation of a network of investigators aimed at assessing the recurrence of IgAN in grafted kidney in Italy looking for factors predictive of the event.

This consortium of 9 Nephrology and Immunogenetics centres collected retrospective data from kidney transplant patients with a biopsy-proven IgAN as a cause of end-stage renal failure to determine their natural history after transplantation and the subsequent clinical course.

\section*{Subjects investigated in an Italian multicentre study}

Adult patients with histological diagnosis of IgAN in native kidney who underwent kidney transplantation in the Italian Transplantation Centres of Turin, Milan, Pavia, Brescia, Florence and Bari between 1984 and 2004 were asked to participate in this study if the entry criteria of recurrence or non-recurrence of IgAN were met.

Recurrent patients were considered those who had a graft biopsy showing IgAN at any time post-transplantation together with urinary signs such as microscopic haematuria and/or proteinuria. We defined non-recurrence as the absence of IgA deposits at a renal allograft biopsy performed less than 6 months before data collection, or serum creatinine $\leq 1.3$ mg/dl, proteinuria $\leq 0.5$ g/day and no haematuria at sampling and at last follow-up. Patients with persistent urinary abnormalities (microscopic haematuria and/or proteinuria $\geq 0.5$ g/day) or signs of graft dysfunction (serum creatinine $\geq 1.3$ mg/dl) without graft biopsy were not enrolled in the study.

For subjects who had serum or cell investigation, samples were collected between January 2001 and December 2006 and non-recurrent patients were
confirmed at last follow-up. Control sera and DNA samples were selected from healthy subjects matched with IgAN patients for gender, age and ethnicity.

The study was performed according to the guidelines and ethical principles for medical research involving human subjects of the World Medical Association Declaration of Helsinki, and informed consent was obtained from each participant.

Data on recurrent IgAN from the Italian multicentre study

Clinical and historical data were collected from 361 patients (291 males, 70 females) with IgAN as original disease which led to dialysis and transplantation.

The recurrence of IgAN in the grafted kidney, demonstrated by renal biopsy in association with significant urinary abnormalities, was detected in 20.5% of the patients (74/361). The median time elapsed between transplantation and IgAN recurrence was 45.5 (range 0.7-210; IQR 15-79) months (Fig. 1, Table II). The development of IgAN within at least 5 years follow-up (which is, according to the literature, a reasonable time allowed for the development of new immune IgA mesangial deposits, resulting in microhaematuria and/or proteinuria) was detected in 18% of cases (51/285). A recurrence of those with follow-up up to 10 years was observed in 39% of patients (69/182). Another 5 patients had a late recurrence of IgAN after a follow-up longer than 10 years. While some IgAN recurrence developed as early as after 1 month after transplantation, most of the recurrences (51/74, 69%) developed within 5 years and others were detected as late as 210 months after transplantation.

It is debatable whether IgAN recurrence influences graft survival. In the series gathered from the Italian consortium, recurrent IgAN had a renal function decline significantly faster than non-recurrent, as detected by the time to survival to the end-point of reaching a serum creatinine of 2 mg/dl with a hazard ratio (HR) of 1.81 and 95% confidence interval (CI) 1.23-4.17, P=0.008 (Fig. 2).

Table II
Clinical and demographic characteristics of the 361 patients who had IgAN as original disease in native kidneys and underwent kidney transplantation (Italian multicentre study on recurrent IgAN)

<table>
<thead>
<tr>
<th></th>
<th>Recurrence (n = 74)</th>
<th>Non-recurrence (n = 287)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>59/15</td>
<td>232/55</td>
<td>NS</td>
</tr>
<tr>
<td>Donor (living/cadaveric)</td>
<td>11/63</td>
<td>35/252</td>
<td>NS</td>
</tr>
<tr>
<td>Age at diagnosis of IgAN in the native kidney (years, median-IQR)</td>
<td>30 (20-40)</td>
<td>31 (24-40)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of dialysis (years, median-IQR)</td>
<td>2.40 (0.92-3.96)</td>
<td>2.65 (1.34-4.58)</td>
<td>NS</td>
</tr>
<tr>
<td>Age at transplantation (years, median – IQR)</td>
<td>39 (31-48)</td>
<td>43 (34-53)</td>
<td>0.05</td>
</tr>
<tr>
<td>Median time of recurrence (months, media, IQR)</td>
<td>45.5 (34-57)</td>
<td>78.50 (IQR)</td>
<td>–</td>
</tr>
<tr>
<td>Age at recurrence (years, median)</td>
<td>39.99 (32-55)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
No significance difference between recurrent and non-recurrent patients was observed as far as several clinical data are concerned (Table II), including gender, age at renal biopsy of IgAN and duration of dialysis treatment before transplantation. Recurrent patients were slightly younger than non-recurrent ones when they received the graft (p<0.05).

Most patients were given steroids and calcineurin inhibitors for basic immunosuppression, and mycophenolate mofetil was used in one third of the patients for various periods of time. Treatment protocols were so variable, particularly for the duration of each drug, that no analysis was practical. No clear difference in immunosuppressive drug regimens was observed between recurrent and non-recurrent patients.

**Clinical Risk Factors for Recurrence of IgAN in Grafted Kidneys**

The analysis of the data gathered from the Italian consortium was initially aimed at understanding whether any of the clinical data available at the time of transplantation could be predictive of IgAN recurrence. The following variables were considered: gender, age at transplantation, origin of the graft (living or cadaveric donor), HLA, age at onset of original disease and its relevant clinical features, such as degree of proteinuria and rapidity of progression from onset to dialysis.

Gender and origin of the graft turned out not to be predictive of IgAN relapse (male versus female gender HR 0.99 (95% CI 0.56-1.8), P=0.97; living versus cadaveric donor HR 0.78 (95% CI 0.38-1.16, P=0.45). In particular, no relationship between living kidney donation and recurrence, which was suspected by some authors, was detected.

An analysis was conducted on some HLA phenotypes that had previously been described in literature as possibly associated to IgAN recurrence after kidney transplantation, in particular HLA-A2; however, in the cohort examined HLA-A2 phenotype was not associated with IgAN recurrence (HR 1.23, 95% CI 0.73-2.01, P=0.44).

Patient age at onset of the original IgAN was analysed and a trend, not statistically significant, was observed of a higher frequency of relapses in those patients who were younger at onset of disease in native kidney (30 years old, HR 0.98, 95% CI 0.58-1.66, P=0.93). The risk of developing recurrent IgAN was significantly greater in patients who had shorter duration of original IgAN disease (HR 2.26, 95% CI 1.08-4.60, P=0.035) (Fig. 3). Patients with a nephrotic proteinuria at onset of IgAN in the native kidney showed an evident, although not statistically significant, trend to a higher rate of IgAN recurrence in the grafted kidney (HR 1.95, 95% CI 0.73-5.44, P=0.17) (Fig. 4).

Another aim of the study was to identify any clinical features, displayed after kidney transplantation, possibly predictive of IgAN recurrence on the graft. Reaching a proteinuria level higher than
1 g/day during the post-transplantation follow-up was highly significantly associated with IgAN recurrence on the graft (HR 4.57, 95% CI 6.83-33.77, P<0.0001) (Fig. 5), as was reaching creatinine levels above 2 mg/dl (HR 2.07, 95% CI 1.25-1.30, P=0.0076).

Performing Cox multivariate analysis using those features that were significantly associated with IgAN recurrence or showed a trend of association, we found that medium time average proteinuria in the first 3 years after transplantation is highly predictive of IgAN recurrence, while age at onset of the original IgAN and its duration shorter than one year before need for dialysis showed borderline levels of statistical significance (Fig. 6).

SEROLOGICAL AND GENETIC RISK FACTORS FOR IgAN RECURRENCE IN GRAFTED KIDNEYS

In the pathogenesis of IgA mesangial deposit formation, a major role is thought to be played by aberrantly glycosylated IgA1 exhibiting defective galactose (Gal) and/or sialic acid (Neu5Ac) content with increased exposure of internal N-acetylgalactosamine (GalNAC) residues of the O-linked carbohydrate side chains of the hinge region. IgA1 molecules with increased exposure of GalNAC tend to autoaggregate or to establish binding with circulating IgG or fibronectin leading to macromolecular IgA complexes. In addition, the enhanced carbohydrate interactions with fibronectin, laminin, and collagen within the mesangial matrix favours the mesangial deposit of aberrantly glycosylated IgA1. Even though human IgAN does not present with a defect of uteroglobulin (UG) speculated in mice, we reported less UG incorporation into IgA-fibronectin complexes in proteinuric than in non-proteinuric IgAN and this property might contribute to diseasing activity.

The abnormal immune response that leads to formation of IgA mesangial deposits as well as the factors favouring disease severity are conditioned by T lymphocyte and mesangial cell activity. Gene polymorphisms influence the levels of some cytokines regulating T helper (Th) response and Th1/Th2 balance, critical for IgA1 glycosylation, as well as lymphocyte and mesangial cell release of pro-flogistic and/or pro-sclerotic mediators. Among the cytokines,
tumour necrosis factor α (TNF-α), a pro-inflammatory cytokine produced by activated monocytes, mesangial cells and Th1 lymphocytes, and interleukin 6 (IL-6), produced by macrophages and mesangial cells activated by Th1 cytokines, are thought to play a key role in IgAN. Th1/Th2 balance is regulated also by interferon γ (IFN-γ) and interleukin 10 (IL-10), released by Th1 and Th2 subsets respectively. Interest is also focused on transforming growth factor β (TGF-β) as a factor favouring progression to renal fibrosis (reviewed in 25). The amount of these cytokines is subject to genetic regulation and several investigations have been recently devoted to investigating the role of these genes in the development and progression of IgAN (reviewed in 26). Similarly the activity of the renin-angiotensin system (RAS), which is frequently activated in progressive IgAN 27, is regulated by several genes, including angiotensin-converting enzyme (ACE), angiotensinogen (AGT) and angiotensin receptor type 1 (AT1R) 28.

In a previous multicentre and multiethnic collaborative study we investigated whether IgA serology differed between recurrent and non-recurrent IgAN 29, but the results failed to prove a clear predictive value for macromolecular IgA. Since then specific tests to detect aberrantly glycosylated IgA1 have become available 16-19 but these assays have not yet been applied to investigating recurrent and non-recurrent IgAN. In a recently published study 30 we investigated the association of several serologic factors (including levels of aberrantly glycosylated IgA1, IgA binding to Fibronectin and to type IV Collagen, IgA-Fibronectin complexes, Uteroglobin incorporated into circulating IgA-Fibronectin complexes) and genetic factors (including cytokine genes single nucleotide polymorphisms and RAS genes polymorphisms) with the recurrence of IgAN in renal transplant recipients.

The Italian consortium investigated 61 patients with IgAN as original disease in the native kidney who progressed to dialysis and transplantation. A recurrence was diagnosed by renal biopsy in 30 out of 61 patients investigated who had IgAN as original disease and the time elapsed from transplantation to histological diagnosis of recurrence was 2.9 years as median. Recurrent and non-recurrent IgAN patients did not differ in age, duration of dialysis before transplantation, time elapsed from transplantation to sampling, or other demographic data.

The cohort of IgAN patients selected, who suffered from a disease so severe as to have progressed to dialysis and transplantation, was characterised by median levels of circulating aberrantly glycosylated IgA1 with increased exposure GalNAc (IgA1 binding to HA and VV) content significantly higher than that

<table>
<thead>
<tr>
<th>Table III</th>
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<tbody>
<tr>
<td>IgA serology in patients with recurrent and non-recurrent IgA nephropathy (IgAN) in the grafted kidney.</td>
</tr>
<tr>
<td>All the patients had a histological diagnosis of IgAN in the native kidney and carried a grafted kidney (IgAN Tx). Recurrence was diagnosed by renal biopsy in 30, and non-recurrence in 31 cases. Serum levels of IgA1 binding to Vicia Villosa (IgA1-VV) or to Helix Aspersa (IgA1-HA) lectins reactive with GalNAc residues of IgA1 indicating degalactosylated/desialylated IgA1; IgA1 binding to Concanavalin Ensiformis (IgA-ConA) lectin reactive with Mannose residues, not reported to be altered in IgAN (control test); IgA-fibronectin (IgA-Fn ) complexes, uteroglobin (UG) incorporated into IgA-Fn complexes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serum levels</th>
<th>Healthy controls</th>
<th>Non-recurrent IgAN</th>
<th>Recurrent IgAN (P value vs. non recurrent)</th>
<th>IgAN Tx patients (P value vs. controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aberrantly glycosylated IgA1: IgA1-VV (note 1)</td>
<td>0.22 (0.18-0.25)</td>
<td>0.26 (0.21-0.36)</td>
<td>0.34 (0.23-0.55) (0.08)</td>
<td>0.30 (0.21-0.45) (0.00)</td>
</tr>
<tr>
<td>Aberrantly glycosylated IgA1: IgA1-HA (note 1)</td>
<td>0.40 (0.09-0.63)</td>
<td>0.74 (0.53-1.10)</td>
<td>0.76 (0.54-0.88) (0.78)</td>
<td>0.75 (0.54-0.94) (0.00)</td>
</tr>
<tr>
<td>IgA1-ConA</td>
<td>1.97 (1.90-2.07)</td>
<td>2.00 (1.79-2.11)</td>
<td>1.79 (1.60-2.03) (0.070)</td>
<td>1.86 (1.68-2.09) (0.002)</td>
</tr>
<tr>
<td>IgA-Fn complexes</td>
<td>0.13 (0.10-0.17)</td>
<td>0.21 (0.14-0.30)</td>
<td>0.22 (0.14-0.29) (0.75)</td>
<td>0.21 (0.14-0.30) (0.002)</td>
</tr>
<tr>
<td>UG incorporated in IgA -Fn complexes</td>
<td>0.63 (0.49-1.08)</td>
<td>0.46 (0.41-1.08)</td>
<td>0.46 (0.42-0.70) (0.620)</td>
<td>0.46 (0.42-1.04) (0.008)</td>
</tr>
</tbody>
</table>

Data are median values and interquartile range. All the results are expressed in optical density (OD) absorbance units.
of the healthy controls, while the levels of IgA1 binding to Con-A via mannose residues were similar to controls (Table III). Circulating macromolecules formed by IgA-Fn aggregates were significantly higher in IgAN patients than in the controls, while the incorporation of uteroglobulin into these complexes was significantly lower in progressive IgAN than in healthy controls. Levels of IgA binding to mesangial matrix components fibronectin or collagen IV were not statistically different between IgAN and healthy controls.

By focusing on serologic difference between IgAN patients with and without recurrence, in general no parameter was significantly different in recurrent and non-recurrent patients. A different trend was detected for aberrantly glycosylated IgA1 binding to Vicia Villosa (IgA1-VV), slightly higher in recurrent patients compared to non-recurrent ones. This test detects IgA1 with greater exposure of GalNAc, thus indicating aberrantly glycosylated IgA1 with defective sialylation and galactosylation of O-linked carbohydrate side chains of the IgA1 hinge region. The fair specificity at ROC analysis of the detection of aberrantly glycosylated IgA1 binding to VV suggests that this test might be of some predictive value for non-recurrence when negative. A possible hypothesis is that fluctuating levels of IgA1, borderline levels of aberrantly glycosylated IgA1, are rendered nephrotoxic when meeting with a suitable immunological environment.

The logistic regression analysis pointed out the protective role against recurrence of TNF-α promoter -308G SNP, which is associated with a high production of TNF-α. TNF-α polymorphisms have been shown to influence the initiation of IgAN in native kidneys31. TNFα plays an important regulatory role in Th1/Th2 balance, limiting the induction of Th2. Moreover, another genetic factor, the IL-10 promoter -1082G, -819C, -592C SNPs which conditions low levels of IL-10, was also found to be associated with protection from IgAN recurrence. In IgAN patients the expression of IL-10 in circulating lymphocytes is enhanced32, and an association of IL-10 gene G-1082A polymorphism with progression of IgAN has been reported, possibly modulated by its anti-inflammatory properties. Since IL-10 down-regulates the synthesis of INFγ and of TNFα, it acts as a powerful regulator of Th1/Th2 balance33.

In conclusion, this study suggested a role in early IgAN recurrence for a combination of SNPs of TNFα and IL-10 which are known to condition Th2 prevalence, while the effect of high levels of aberrantly glycosylated IgA1 was of borderline relevance.

**CONCLUSION**

Recent analyses tend to present IgAN recurrence as a time-dependent phenomenon, which develops in 20% of cases within 4 years, in almost 50% at 10 years, and in the majority of patients after 20 years of graft survival. Although the risk increases over time, recurrence does not involve the totality of the patients, and outcome is variable, from clinically quiescent disease to progressive graft dysfunction. However, it is obvious that the earlier the recurrence, the higher the risk that IgAN may lead to deterioration of graft function in the long-term. From the data gathered by the Italian consortium for investigating the recurrence of IgAN in the grafted kidneys, recurrence of IgAN was frequent, affecting more than one quarter of patients after post-transplant follow-up longer than 5 years and it was associated with faster decline of renal function. Recipient risk factors are thought to play the major role, even though none of the many investigated belonging to data before renal transplantation provided clear-cut evidence of being significantly predictive of future recurrence of IgAN in the grafted kidney. Gender, age, source of graft, and HLA do not seem to influence the recurrence. Genetic factors conditioning a prevalence of the Th2 subset seem to play a role in the recurrence, in association with high levels of aberrantly glycosylated IgA1. The development and persistence of proteinuria during the post-transplant follow-up is the most sensitive predictive index for IgAN recurrence.

**Conflict of interest.** None declared.

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Renal transplantation in patients with primary IgA nephropathy: risk of recurrence and renal allograft loss

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