



## Leuvense Samenwerkende Groep Niertransplantatie

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## GRIEPSEIZOEN

Geachte collega,

Met de intrede van de winter is deze nieuwsbrief integraal gewijd aan infecties na niertransplantatie.

Prof. Dr. **Willy Peetermans** schreef voor u een 'state of the art'-artikel over vaccinaties bij niertransplantpatiënten. Het biedt u praktische tips voor de klinische praktijk.

De dienst Nierziekten, de dienst Infectieziekten (Prof. Dr. W. Peetermans) en de dienst Virologie (Prof. Dr. M. Van Ranst) sloegen overigens de handen in elkaar voor een omvangrijk multicentrisch project. Het bestudeert in detail de veiligheid en de efficiëntie van griepvaccinatie bij niertransplant- en hemodialysepatiënten. De inclusiefase werd net afgesloten en de studieresultaten vindt u in één van de LSGN-nieuwsbrieven van 2004.

Dr. **Annemie Vandermarliere** bespreekt in een minutieuze retrospectieve analyse het optreden van tuberculose na niertransplantatie. Zij toont aan dat de incidentie van tuberculose over de jaren heen niet gestegen is ondanks het gebruik van krachtigere immuunsuppressiva zoals tacrolimus, mycophenolaat mofetil en sirolimus. Tuberculose na niertransplantatie blijft dus gerelateerd aan de cumulatieve dosis corticosteroiden.

In de vorige nieuwsbrief werd u gevraagd een **antwoordkaart** terug te sturen die peilde naar uw interesse in deelname aan het project 'Protocolbiopsies'. Helaas sloeg de wet van Murphy toe en werd het kaartje vergeten. Onze oprechte excuses hiervoor.

Mag ik u vragen om alsnog de antwoordkaart te vervolledigen en terug te zenden?

Uw antwoorden en de praktische uitwerking van het project zullen dan worden besproken tijdens de eerste LSGN op 29 januari 2004.

Tot slot wensen de stafleden Nefrologie ieder van u een zalig kerstfeest en het allerbeste voor het nieuwe jaar!

**Prof. Dr. Y. Vanrenterghem**



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# Wetenschappelijke informatie

## Vaccinaties bij de orgaantransplantpatiënt

**P**atiënten die een orgaantransplantatie ondergaan, hebben een verhoogde vatbaarheid voor infecties. Die hebben bij hen ook vaak een ernstiger verloop. De leeftijd, de onderliggende aandoening en vooral de immunosuppressieve therapie zijn de voornaamste risicofactoren. Voor een aantal infecties bestaat de mogelijkheid van preventie door vaccinatie. Het succesverhaal van vaccinatie tegen kinderziekten zoals polio, mazelen, rubella en Haemophilus influenzae type B is algemeen bekend. Ook bij volwassenen en bejaarden bleek vaccinatie een effectief middel ter preventie van potentieel ernstige aandoeningen zoals tetanus, griep en invasieve pneumokokkeninfecties. Naast de basisvaccinaties zijn er nog de gerichte indicaties zoals vaccinaties bij specifieke beroepsrisico's of bij reizen naar de tropen. Internationale en nationale wetenschappelijke instanties hebben praktijkrichtlijnen voor vaccinaties gepubliceerd. Zo werden in 2002 in ons land de aanbevelingen voor vaccinaties bij volwassenen en kinderen geactualiseerd door de Hoge Gezondheidsraad ([http://www.health.fgov.be/CSH\\_HGR/lijst\\_van\\_advies\\_en\\_brochures.htm](http://www.health.fgov.be/CSH_HGR/lijst_van_advies_en_brochures.htm)). Dit artikel biedt u een samenvatting van de wetenschappelijke gegevens over vaccinaties bij orgaantransplant- en vooral niertransplantpatiënten, die in enkele recente overzichtsartikels werden beschreven.

### T-cel afhankelijke antigenen

De vaccinologie maakt een onderscheid tussen T-cel afhankelijke antigenen (bv. de eiwitantigenen van influenza) en T-cel onafhankelijke antigenen (bv. de polysaccharide-antigenen van het pneumokokkenkapsel). Bij patiënten met een cellulaire immunodeficiëntie is de immuunrespons vooral zwakker tegen T-cel afhankelijke antigenen. Bij medicamenteus geïnduceerde T-cel immunodeficiëntie zijn de dosering en de duur van de immunosuppressieve behandeling de voornaamste parameters. Deze stelling refereert echter vooral aan corticosteroiden. In hoeverre dit ook geldt voor de nieuwere immunosuppressiva is niet duidelijk.

### Veiligheid van levend afgezwakte vaccins

Vaccins zoals het mazelen-bof-rubella vaccin, het gele koorts-vaccin en het niet langer beschikbare orale polio-Sabin-vaccin, zijn levend afgezwakte vaccins. Zij zijn gecontraïndiceerd bij patiënten die meer dan 10 mg prednisone/dag gedurende 2 weken krijgen of meer dan 700 mg prednisone in totaal bij aaneengesloten verbruik. In de USA wordt het criterium van meer dan 20 mg prednisone/dag gebruikt. Men neemt aan dat deze contraïdicatie geldt tot ten minste 3 maanden na het staken van deze medicatie.

Levend afgezwakte vaccins zijn ook gecontraïndiceerd bij patiënten die een combinatie van 2 of meer immunosuppressiva nemen, zoals de orgaantransplantpatiënt. Vaccins op basis van gedode micro-organismen, gezuiverde antigenen epitopen of geïnactiveerde toxines zijn veilig, zowel wat

betreft nevenwerkingen als wat betreft het risico van reëctie.

### Antistofrespons en klinische protectie

De grootte van de antistofrespons is niet voor alle vaccins een goede surrogate marker voor hun klinische bescherming. Voor sommige vaccins (bv. pneumokokken) is de correlatie tussen antistoftiter en klinische effectiviteit minder sterk dan voor andere (bv. hepatitis B). Men neemt aan dat cellulaire immunomechanismen ook een bijdrage leveren tot de klinische werkzaamheid van bepaalde vaccins. In hoeverre de verminderde antistofrespons en een cellulaire immunodeficiëntie leiden tot een verminderde klinische protectie bij orgaantransplantpatiënt, is niet goed uitgeklaard. Studies over de klinische bescherming door vaccinaties vereisen zeer grote (zelfs irreële) patiëntenpopulaties en zijn in de praktijk niet haalbaar. Bleken vaccins effectief bij de immunocompetente volwassenen, genereren ze een voldoende antistofrespons en zijn ze veilig? Dan lijkt het verantwoord ze ook bij orgaantransplantpatiënten aan te bevelen. In de regel zal men vaccinatie uitstellen tot 6 maanden na de transplantatie.

### Herhaling van de basisvaccinaties

**Tetanus/difterie** - Een routinematige herhalingsvaccinatie (Td in aangepaste dosering voor volwassenen) om de 10 jaar wordt aanbevolen bij alle patiënten die ooit een volledige basisvaccinatie kregen. Is de laatste herhalingsdosis meer dan 20 jaar geleden? Dan worden 2 toedieningen met 6 maanden interval aanbevolen. Als het onzeker is dat er



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ooit een volledige basisvaccinatie gebeurde, dan wordt een volledige hervaccinatie met 3 dosissen voorgesteld. De immunogeniciteit van het tetanusvaccin is afdoende indien toegediend tenminste 6 maanden na transplantatie. De antistoftiters lijken wel sneller te dalen dan bij een controlegroep maar blijven boven de protectieve drempel. Het vaccin wordt goed getolereerd (in een studie bij niertransplantpatiënten zelfs beter dan bij de controles). Geen enkel geval van rejectie na vaccinatie werd gerapporteerd.

**Polio** - Een herhalingsvaccinatie met het gedode polio Salk-vaccin is alleen aangewezen bij risicopersonen (bv. ter gelegenheid van een tropenreis).

**Hepatitis B** - Bij patiënten met protectieve antistoftiters (> 10 mU/L) na een hepatitis B-vaccinatie voor transplantatie wordt een herhalingsdosis aangeraden als de titer daalt onder deze drempel. Werden transplantpatiënten vooraf niet gevaccineerd of vertoonden ze geen antistofrespons (bv. tijdens hemodialyse)? Dan wordt een vaccinatieschema met 3 dosissen (t = 0, 1 & 6 maand) aanbevolen met controle van de antistoftiter 1 maand na de laatste toediening. Men zal bij voorkeur gebruik maken van het hooggedoseerde hepatitis B vaccin. Toch zal ook dan slechts 10-30% van deze patiënten protectieve antistoftiters bereiken. Het vaccin wordt goed getolereerd door orgaantransplantpatiënten en er zijn geen meldingen van vaccinatie-geïnduceerde rejecties.

### Vaccins voor volwassenen

**Influenza** - Een jaarlijkse vaccinatie met het geïnactiveerde influenzavaccin (in de door de WHO aanbevolen samenstelling) wordt sterk aanbevolen bij orgaantransplantpatiënten. Bij deze patiënten leidt influenza tot een hoog aantal pulmonale en extrapulmonale verwickelingen. Meer dan 30% van de orgaantransplantpatiënten met influenza ontwikkelen een pneumonie met een mortaliteit van 20%. Bovendien wordt vaak een achteruitgang van de orgaanfunctie waargenomen. Ook de excretie van influenzavirus is verlengd t.o.v. de controles. De immunogeniciteit van de 3 vaccincomponenten lijkt goed bij niertransplantpatiënten. Meerdere studies toonden

aan dat 90% van de patiënten protectieve antistoftiters bereikten. Niertransplantpatiënten onder ciclosporine A hadden echter significant lagere titers dan patiënten onder azathioprine. Ook de combinatie van mycophenolaatmofetil met ciclosporine en corticosteroiden resulteerde in lagere titers na influenzavaccinatie. Slechts 30-70% van multi-orgaantransplantpatiënten hadden een protectieve antistofrespons. Evidentie dat een 2de vaccindosis nuttig zou zijn bij orgaantransplantpatiënten is niet beschikbaar.

Het griepvaccin wordt goed getolereerd. Het is onmogelijk om influenza te ontwikkelen als direct gevolg van de vaccinatie. Er zijn enkele sporadische rapporten van rejectie na vaccinatie, maar in klinische studies was er geen verschil met placebo-behandelde patiënten.

Influenzavaccinatie wordt ook aanbevolen bij nauwe contactpersonen van transplantpatiënten en (para)medisch personeel, die als bron van de influenzabesmetting voor de immuundeficiënte patiënt kunnen fungeren.

**Pneumokok** - Na vaccinatie met het 23-valent kapselpolysaccharide pneumokokkenvaccin hebben 80 tot 90% van de niertransplantpatiënten (met 2- of 3-ledige immunosuppressie) een significante antistofrespons, die vergelijkbaar is met deze van immunocompetente personen. Toch lijken de antistoftiters wel sneller te dalen. Hoge dosis corticosteroiden lijkt de immunogeniciteit ook negatief te beïnvloeden. Het vaccin wordt goed getolereerd en er zijn geen meldingen van rejectie na vaccinatie. Bij immunocompetente volwassenen biedt het vaccin een bescherming van 70% tegen invasieve pneumokokkeninfecties zoals pneumokokkensepsis. Vaccinatie met het 23-valent pneumokokkenvaccin wordt aanbevolen bij alle orgaantransplantpatiënten met een revaccinatie na 5 tot 7 jaar.

### Conclusie

Een actieve vaccinatiepolitiek maakt deel uit van de klinische follow-up van orgaantransplantpatiënten. Een goede coördinatie met de behandelende huisarts moet hierbij worden nagestreefd.

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# Klinische studie

## Mycobacterial infection

### after renal transplantation in a Western population

#### **ABSTRACT** (Transpl Inf Dis 2003; 5:9-15)

Mycobacterial infection is a serious opportunistic infection in renal transplant recipients. The incidence is higher in developing than in developed Western countries. This study is a single centre retrospective review of the records of 2502 renal transplant recipients in Belgium. Fourteen cases of mycobacterial infection (9 *Mycobacterium tuberculosis* and 5 atypical mycobacterial infection) were diagnosed. The time interval between transplantation and diagnosis was  $64 \pm 80$  months (mean  $\pm$ SD, range 5-188) for *Mycobacterium tuberculosis* and  $92 \pm 75$  months (range 14-209) for atypical mycobacterial infection. The localization of *Mycobacterium tuberculosis* was pulmonary/pleural in 67% and extrapulmonary in 33%. The atypical mycobacterial infections were located in skin, tendons and joints. Eight patients received IV prednisolone pulse therapy for acute rejection long before the time of mycobacterial infection. The initial antimycobacterial therapy consisted of a combination of isoniazid, rifampicin and ethambutol in all patients. In patients with *Mycobacterium tuberculosis* infection, a good response to antimycobacterial therapy was obtained. In patients with atypical mycobacterial infection, initial treatment was successful in 3 out of 5 patients, in one patient recurrence was diagnosed and in another patient, who is still under treatment at present, the initial treatment was adjusted after identification of the atypical *Mycobacterium* and its antibiogram.

Summary. The incidence of mycobacterial infection after renal transplantation did not increase with newer immunosuppressive therapy. The major risk factor is the total dose of corticosteroids. All patients responded well without major reductions in immunosuppressive therapy. Chemoprophylaxis for high-risk patients still is recommended.

*Keywords: corticosteroids, immunosuppressive therapy, transplantation and tuberculosis*

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**T**here is an increased risk of developing tuberculosis in immunosuppressed patients. Tuberculosis also remains one of the most serious bacterial infections after transplantation<sup>(1)</sup>. The world-wide incidence of tuberculosis after solid-organ transplantation is approximately 0.8%<sup>(2)</sup>. In developed Western countries, the reported prevalence of tuberculosis in renal transplant recipients ranges from 0.35 to 4% , but much higher figures (up to 14.6%) have been reported in developing countries<sup>(1-5)</sup>. Renal transplant recipients also have a higher risk of developing infections with atypical mycobacteria. The immunosuppressive prophylactic therapy has changed substantially the last two decades, with the introduction of potent immunosuppressants such as cyclosporine, tacrolimus, mycophenolate mofetil and sirolimus. It is not clear until today what type of immunosuppressive therapy is more likely to predispose to mycobacterial infection after renal transplantation.

The aim of this study was to evaluate the influence of immunosuppressive and antimycobacterial therapy on incidence and outcome of mycobacterial infections and the impact on allograft function in a Western population.

#### **MATERIALS AND METHODS**

Between 1963 and 2001, 2502 renal transplantations (1482 male, 1020 female, 2489 cadaveric, 13 living-related donor) were performed in our hospital (pre-cyclosporine A (CsA) era: 505, patients induced with CsA: 1684, patients induced with tacrolimus (FK506): 313). Prior to transplantation 2118 patients underwent hemodialysis and 126 patients peritoneal dialysis. 89.6% were first graft recipients, 9.4% second graft recipients, 0.9% third graft recipients and 0.1% fourth graft recipients. Before 1983 the induction immunosuppressive protocol consisted of azathioprine (Aza) (2 mg/kg/d) plus corticosteroids (CS) (IV prednisolone 500 mg pre-transplantation followed by 16 - 24 mg/day tapered to 0 - 4 mg/day). After this date, double or triple therapy protocols with CsA were used. In patients taking CsA, the dose was adjusted to obtain plasma 12-hour trough levels of 100 - 250 ng/ml. according to time after transplantation. After 1993 the standard immunosuppressive prophylactic therapy

gradually included therapy with FK506 and/or mycophenolate mofetil (MMF). The dose of FK506 was adjusted to obtain plasma 12-hour trough levels of 5 - 15 ng/ml according to time after transplantation. Patients taking FK506 in combination with MMF, received 1 g MMF per day, those taking CsA received 2 g MMF per day. Induction was started 4 hours prior to transplantation in all patients with Aza (1 mg/kg) - MMF (1 g), IV prednisolone (500 mg) and CsA (8 mg/kg) - FK506 (0.2 mg/kg). In the pre-CsA era all patients received polyclonal antibodies (antithymocyte globuline (ATG) or antilymfocyte serum (ALS)) together with CS + Aza. Until the introduction of MMF and FK506, patients

received ALS/ATG as additional induction therapy for high-risk patients such as T-cell antibodies more than 50% or a second (or next) renal transplantation after losing their previous allograft within 12 months following transplantation because of immunological events. Recently, polyclonal antibodies were substituted by monoclonal antibodies (anti-IL2

There is an increased risk of developing tuberculosis in immunosuppressed patients.

receptor antibodies: Simulect(r) and Zenapax(r)) for this indication.

As first-line antirejection therapy high dose IV prednisolone (150 - 200 mg) during 5 days for the first episode of acute rejection was used. A subsequent episode of acute rejection was treated with steroids or polyclonal antibodies (Orthoclone(r) (OKT3) or ATG). The third episode of acute rejection was routinely treated with high dose IV prednisolone.

We retrospectively analysed all patients' files for diagnosis of mycobacterial infection following renal transplantation. We reviewed patients' charts on demographic characteristics, immunosuppressive and antituberculous therapy protocols, response to therapy and the outcome of the mycobacterial infection and of the allografts. The clinical suspicion was low-grade fever, pulmonary signs and symptoms and skin/soft tissue/joint abnormalities. The diagnosis of mycobacterial infection was culture-proven from relevant specimens, except for one patient: sputum, bronchial aspirate or broncho-alveolar lavage fluid for pulmonary disease, urine for urinary tract disease and tissue biopsies for soft tissue and bone disease. One patient was diagnosed with mycobacterial infection on clinical suspicion, suggestive radiology and good response to antituberculous therapy.

## RESULTS

### Demographics and medical history

Mycobacterial disease after renal transplantation was diagnosed in 14 of 2502 renal transplant recipients (prevalence: 0.56%). Before the introduction of CsA (1983) the diagnosis of tuberculosis was made in 2 patients (0.4%), in the time period between 1983 and 1994 the diagnosis of tuberculosis was made in 2 patients (0.19%), the diagnosis of atypical mycobacterium infection was made in 2 other patients (0.19%) and after 1994 5 patients were diagnosed with tuberculosis (0.53%) and 3 with atypical mycobacterium infection (0.32%). These differences between time periods were statistically not significant (SAS: PROC FREQ; Fisher Exact Test). Eight patients were male, 6 were female; the

age at the time of diagnosis was  $49.6 \pm 16.8$  years (mean  $\pm$  SD, range 20-70).

Nine patients had a Mycobacterium tuberculosis infection (0.36%) and five patients (0.20%) an infection with atypical mycobacteria. The demographic characteristics of these patients are given in table 1. All patients with the diagnosis of mycobacterial infection underwent haemodialysis prior to renal transplantation for a period of  $33.4 \pm 31.6$  months (mean  $\pm$ SD, range 5-104).

The time interval between transplantation and the diagnosis of mycobacterial infection was  $64 \pm 80$  months (mean  $\pm$  SD, range 5-188) in patients with a Mycobacterium tuberculosis infection and  $92 \pm 75$  months (mean  $\pm$  SD, range 14-209) in patients with an atypical mycobacterial infection (table 2). The site of tuberculosis disease was pulmonary/pleural in 67% and extrapulmonary in 33% of the patients. The infections with atypical mycobacteria were located in skin, tendons and joint (figure 1).

Figure 1: Skin disease due to atypical mycobacterial infection in a renal transplant patient.



Risk factors for mycobacterial infection were present in several patients<sup>(6)</sup>:

- Significant radiological abnormalities suggestive for previous tuberculosis disease were present in one patient;
- two were from noncaucasian ethnic background;

(c) and/or eight had other immunosuppressive conditions like protein-calorie malnutrition, ... correlated with increased risk for mycobacterial infections (table 3 and section net state of immunosuppression):

(d) one patient had a history of previous Mycobacterium tuberculosis infection that was adequately treated 28 years prior to transplantation; after transplantation she developed an infection with atypical mycobacteria.

Table 1. Demographic characteristics and primary renal disease

Age (years)		49.6	(range, 20-70)
Gender (n)	male	8	(57%)
	female	6	(43%)
Race (n)	Caucasian	12	(86%)
	non-Caucasian	2	(14%)
Primary renal disease (n)	chronic glomerulonephritis	7	(50%)
	renovascular disease	1	(7%)
	ADPKD	3	(22%)
	diabetic nephropathy	1	(7%)
	interstitial nephritis	2	(14%)

ADPKD : Autosomal dominant polycystic kidney disease

Table 2. Diagnosis of mycobacterial infection after renal transplantation.

Patient n°	Age / sex (years)	Time after transplantation (months)	Organism	Location
1	54 / F	161	M. tuberculosis	lung
2	23 / M	12	M. tuberculosis	pleura
3	69 / M	11	M. tuberculosis	lung
4	44 / F	162	M. tuberculosis	intestine (ileum)
5	51 / M	10	M. tuberculosis	bone (rib)
6	20 / M	10	M. tuberculosis	lung
7	44 / M	5	M. tuberculosis	lung
8	64 / F	188	M. tuberculosis	urinary tract
9	43 / M	17	M. tuberculosis	lung
10	67 / F	68	M. chelonae	tendon
11	60 / F	118	M. chelonae	skin
12	28 / M	53	M. xenopii	bone / tendon
13	58 / M	14	atypical M.	skin
14	70 / F	209	M. chelonae	skin

Table 3. Associated risk factors for opportunistic infection.

Patient n°	BMI < 20	Uraemia >90 mg/dL	CMV	EBV	HBV	HCV	HIV	Alcoholic Cirrhosis	DM	Neutropenia <1800/mm <sup>3</sup>	Lymphopenia <1000/mm <sup>3</sup>
1	+	-	-	-	+	-	-	-	-	-	-
2	+	+	-	-	-	-	-	-	-	-	-
3	-	+	-	-	-	-	-	-	-	-	+
4	-	-	+	+	+	+	-	-	-	-	+
5	-	+	+	-	-	+	-	-	+	-	-
6	-	-	-	-	-	-	-	-	-	-	-
7	-	-	-	-	+	-	-	-	-	-	-
8	+	+	-	-	+	-	-	-	-	-	-
9	+	+	+	+	-	-	-	-	-	-	+
10	-	-	-	-	+	-	-	-	-	-	-
11	-	-	-	-	-	+	-	-	-	-	-
12	+	-	-	-	+	-	-	-	-	-	-
13	+	-	+	+	-	+	-	-	+	-	-
14	-	-	-	-	-	-	-	-	-	-	-

CMV: cytomegalovirus; EBV: Epstein-Barr virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; DM: diabetes mellitus

In 53 of all renal transplant patients a Mycobacterium tuberculosis disease was diagnosed and treated prior to transplantation. All these patients received isoniazid prophylaxis at the time of transplantation and none of them developed a recurrence of Mycobacterium tuberculosis disease. None of the patients with mycobacterial disease after renal transplantation received isoniazid prophylaxis after transplantation.

### Net state of immunosuppression

The induction immunosuppressive therapy consisted of CS + CsA + Aza in 2 patients, CS + Aza in 5 patients, CS + CsA in 5 patients and CS + CsA + MMF in 2 patients. At the time of diagnosis, immunosuppression consisted of CS + Aza in 5 patients, CS + CsA in 7 patients and CS + CsA + MMF in 1 patient. One patient lost his graft before diagnosis of mycobacterial infection. At the moment of writing, none of the patients receiving FK506 or sirolimus were diagnosed with mycobacterial infection after renal transplantation.

The doses of immunosuppressive drugs at the time of diagnosis were  $1.54 \pm 0.1$  mg/kg/day (mean  $\pm$  SD, range 1.4-1.65) for Aza,  $0.04 \pm 0.0$  g/kg/day (mean  $\pm$  SD, range 0.037-0.04) for MMF and  $0.125 \pm 0.109$  mg/kg/day (mean  $\pm$  SD, range 0.06-0.4) for prednisolone. The 12-hour trough level of CsA at the time of diagnosis was  $137 \pm 29$  ng/ml (mean  $\pm$  SD, range 100-200).

Three of the 14 patients had received induction therapy with polyclonal antibodies: ATG (1 patient) or ALS (2 patients) (table 3). Eight of the 14 renal transplant recipients (57%) had experienced an allograft rejection preceding the mycobacterial infection treated with IV prednisolone (total dose of  $1728 \pm 1337$  mg, range 800-5100).

In both patient groups, the mycobacterial infection was diagnosed earlier in those receiving double immunosuppressive therapy with CS + CsA (mean:  $50 \pm 74$  months, range 11-161 months in tuberculosis disease, mean  $45 \pm 28$  months, range 14-68 months in atypical mycobacterial disease) than those with CS + Aza (mean:  $59 \pm 89$  months,

range 5-162 months in tuberculosis disease, mean:  $164 \pm 64$  months, range 118-209 months in atypical mycobacterial disease).

As shown in table 3, only 2 patients lacked risk factors usually associated with increased risk for opportunistic infections after transplantation (either as an expression of decreased immunity or inducing immunomodulatory effects itself) were absent; in 9 at least 2 of these risk factors were present, normally classified as 'chronic ne'er-do-well' patients.

### Antimycobacterial therapy

Combined antimycobacterial therapy with 3 drugs was administered in the 9 patients with Mycobacterium tuberculosis disease. They received isoniazid 5 mg/kg/day (max 300 mg/day), rifampicin 10 mg/kg/day (max 600 mg/day) and ethambutol 15-25 mg/kg/day. In one of these 9 patients also pyrazinamid 30 mg/kg/day (max 2 g/day) was administered during the first 3 weeks.

Combined antimycobacterial therapy with 3 drugs (isoniazid, rifampicin and ethambutol) was the initial and permanent therapy in 4 of the 5 patients with an atypical mycobacterial infection. A fifth patient (patient n° 11) with a Mycobacterium chelonae infection was first treated with claritromycin, amikacin and ofloxacin and was then put on levofloxacin and ethambutol.

Treatment duration mounted  $19.7 \pm 19.7$  months (mean  $\pm$ SD, median: 12 months, range 2-69) for isoniazid,  $10.8 \pm 8.2$  months (mean  $\pm$ SD, median: 12 months, range 2-27) for rifampicin and  $7.7 \pm 5$  months (mean  $\pm$ SD, median: 9.5 months, range 2-14) for ethambutol.

As a consequence of starting antimicrobial therapy, the dose of CsA increased from  $188 \pm 65$  to  $475 \pm 184$  mg/day (+253%) to achieve equal CsA trough levels (pre mycobacterial disease:  $137 \pm 29$  ng/mL; post mycobacterial disease:  $112 \pm 19$  ng/mL). The dose of methylprednisolon was reduced in two patients at the time of diagnosis of mycobacterial infection and stopped in one of them two months after the time

of diagnosis. In the other patient also MMF was stopped at the time of diagnosis of the mycobacterial infection.

### Outcome

In all patients with *Mycobacterium tuberculosis* infection a good response to the antimycobacterial therapy was obtained with complete cure in 8/9 patients (table 4). In the patients with an atypical mycobacterium infection, treatment was successful in 3 out of 5. In one patient a recurrence was diagnosed 10 months after withdrawal of the antimycobacterial treatment (triple therapy during 12 months and afterwards double therapy during another 12 months), another patient is still under treatment at present (9 months therapy with levofloxacin and ethambutol).

As far as allograft function is concerned, no episodes of acute rejection occurred after the diagnosis of the mycobacterial infection. Over a period of  $95 \pm 102.7$  months (mean  $\pm$  SD, range 9-318) of follow-up since the diagnosis of the mycobacterial infection, serum creatinine increased from  $1.3 \pm 0.53$  mg/dl (mean  $\pm$  SD, range 0.7-2.4) to  $1.8 \pm 0.9$  mg/dl

(mean  $\pm$  SD, range 0.66-3.09) in 8/14 patients. Six patients of them evolved to ESRD necessitating haemodialysis: two (patient n° 3 and 9) at the time of the mycobacterial infection due to recurrence of primary renal disease (membranoproliferative glomerulonephritis type I), two (patient n° 2 and 4) due to chronic rejection 66 and 68 months after diagnosis of the mycobacterial infection, 1 (patient n° 6) due to recurrence of IgA nephropathy 15 years after diagnosis of the mycobacterial infection and 1 (patient n° 5) returned to haemodialysis 3 months after transplantation because of an acute rejection, in this last patient tuberculosis was diagnosed 7 months after transplantectomy and return to haemodialysis. Two of these 6 patients received a new renal allograft after favourable response to the antimycobacterial treatment.

None of the patients with an atypical mycobacterium infection developed end stage renal disease. We did not find a relationship between the development of ESRD and the mycobacterial infection. Neither did one of the patients lose his allograft due to the antimycobacterial treatment.

Table 4. Immunosuppressive therapy and outcome.

Patient	Immunosuppression before Tx	Tx Induction MD	n AR episodes before Tx	Outcome	Renal outcome
1	/	/	1	R	/
2	/	/	2	R	ESRD due to CR
3	/	/	1	R	ESRD
4	/	ALS	1	R	ESRD due to CR
5	/	/	3	R	ESRD due to AR
6	/	/	0	R	ESRD + re-TX
7	CYC	/	1	R	/
8	/	/	0	R	/
9	/	ATG	0	R	ESRD + re-TX
10	/	/	0	R	/
11	CYC	ALS	1	R	/
12	CYC	/	6	recurrence	/
13	/	/	0	R	/
14	CYC	/	0	R	/

n: number; AR: acute rejection; R: remission; ESRD: end-stage renal disease; CR: chronic rejection; Tx: transplantation; ALS: anti-lymphocyte serum; ATG: anti-thymocyte globulin; CYC: cyclophosphamide, MD: mycobacterial disease

## DISCUSSION

We found *M. tuberculosis* infection in 0,36% and atypical mycobacterial infection of skin or tendon in 0.20% (incidence) of our renal transplant population.

It has been suggested that, in countries where the incidence of *Mycobacterium tuberculosis* is going down, the relative frequency of infection with atypical mycobacteria is rising<sup>(7)</sup>. The increasing numbers of immunosuppressed patients in Western populations may further add to the increasing incidence of infections with atypical mycobacteria.

The risk for opportunistic infections in transplant recipients is determined by the epidemiologic exposure and the net state of immunosuppression<sup>(2)</sup>. Concerning the epidemiologic exposure, one third of our haemodialysis patients had a positive tuberculin skin test and 47,8% a positive tuberculin skin test and/or radiological evidence of tuberculosis<sup>(8)</sup>. However, the mean age of this population was 69 years compared with 50 years in the present study, but the figures in haemodialysis are probably underestimated because of the uraemic immune defect. In the majority of patients, risk factors for mycobacterial infection were present<sup>(6)</sup>. Factors affecting the net state of immunosuppression seemed to be very important: eight patients had a viral infection, six patients a body mass index (BMI) below 20 and five patients presented with an uraemia higher than 90 mg/dl.

Whether the type of immunosuppressive drug is an important factor predisposing to mycobacterial infection in transplant patients has not been established<sup>(1,3,9-12)</sup>. In the present study, it is obvious that all patients received high dose of CS. This suggests that the suppression of macrophage function by steroids may be more important than IL-2 suppression by more selective immunosuppressive drugs in triggering mycobacterial infections. Several studies have shown that CS inhibit the ability to develop adequate intracellular microbactericidal mechanisms<sup>(13, 14)</sup> and also significantly inhibit the production of IL-12 by macrophages, a cytokine that is extremely potent in enhancing IFN-gamma and inhibiting IL-4 synthesis in T cells<sup>(15)</sup>. The fact that with the use of

more potent T-cell immunosuppression (MMF, FK506, sirolimus) the incidence of mycobacterial infection did not increase, seems to confirm this hypothesis<sup>(4)</sup>.

In spite of the continuation of immunosuppressive therapy, we found a good response to the antimycobacterial therapy. In only 2 patients the immunosuppressive therapy (steroids) was reduced at the time of the diagnosis of the mycobacterial infection; as far as CsA was concerned, similar trough level before and after diagnosis were aimed. No difference in outcome was noted, compared with those in which immunosuppressive therapy was not reduced. Therefore major reductions of immunosuppressants in order to obtain a good outcome of the mycobacterial infection do not seem necessary. Nevertheless in patients with disseminated tuberculosis, dose reductions are recommended<sup>(16)</sup>.

Isoniazid prophylaxis following kidney transplantation is controversial. In some studies, isoniazid prophylaxis was found to be beneficial. The American Thoracic Society recommends that prophylaxis be based on tuberculin skin testing of the recipients, accepting > or = 5 mm of induration as positive<sup>(17)</sup>. However, anergy to tuberculin is known to occur in up to 70% of transplant recipients due to impaired cell-mediated immunity. In 53 recipients of our centre a *Mycobacterium tuberculosis* disease was diagnosed and treated properly prior to transplantation. All these patients received isoniazid prophylaxis at the time of transplantation and none of them developed a recurrence of *Mycobacterium tuberculosis* disease.

We conclude that the incidence of *Mycobacterium tuberculosis* infection after renal transplantation has not increased with the use of newer and more potent immunosuppressive therapy. All patients with mycobacterial disease have been treated with higher cumulative doses of corticosteroids compared with the standard transplant patient. All mycobacterial infections responded well to antimycobacterial treatment without major reductions in immunosuppressive therapy. Chemoprophylaxis to prevent *Mycobacterium tuberculosis* disease is recommended for high risk patients after renal transplantation.

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## Agenda

**20 januari 2004**

**Vergadering LSGN (gezamenlijke LOK)  
Restaurant Arenberg, Heverlee**

**5-8 februari 2004**

**New Trends in Immunosuppression  
Salzburg, Oostenrijk**

**14-19 mei 2004**

**American Transplant Congress  
Boston, USA**

**15-18 mei 2004**

**EDTA  
Lissabon, Portugal**