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Quadruple immunosuppression including a new IL-2-receptor antibody and the incidence of infections after liver transplantation

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Immunosuppression is a primary concern after orthotopic liver transplantation (OLT). On the one hand, the graft is at jeopardy through acute or chronic rejection, and on the other, immunosuppression and antirejection therapy increase the risk of infectious complications. Effective immunosuppression therefore should prevent rejections without leading to a high rate of infections, bearing in mind the fact that infections and infection-related complications are the most frequent causes of early death after liver transplantation [1]. With more specific immunosuppression the infectious complications can potentially be minimized. Antithymocyte globulin (ATG) and the first monoclonal antibody OKT3 immunosuppression are non-specific [4]. The replacement of these antibodies in a quadruple immunosuppressive regimen with the new monoclonal IL-2R antibody BT 563 [3] probably reduces the early infection rate. We report on our first experience with BT 563. The incidence of infection was compared with a historical control group with ATG.

Key words: Liver transplantation – Infection – IL-2-receptor antibody – Immunosuppression

Materials and methods

A total of 103 liver transplantations were performed in 98 patients. Between April and September 1990, 33 recipients were treated with BT 563, and compared with 70 consecutive recipients treated with ATG as historical controls. In the BT 563 group no retransplantation was necessary. The median age of the patients was 41 years. In the ATG group there were 65 patients with a median age of 44 years. Five retransplantations were necessary in three patients due to relapsing fulminant hepatitis B (3) and INF (2). Concerning the other indications both groups were comparable.

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Quadruple immunosuppression consisted of steroids, cyclosporin A, azathioprine and rabit antithymocyte globulin (ATG, Fresenius) or the monoclonal IL-2R antibody BT 563 (Biotest). BT 563 was administered as a daily dose of 10 mg IV from day 0 to day 12. In the control group ATG was given from day 0 to day 7 at 5 mg/kg bodyweight IV.

Effects and side effects were diagnosed according to standard procedures. The diagnosis of rejection was established on the basis of pathological changes in liver function tests, clinical signs and histological findings.

Infection prophylaxis remained unchanged in both groups. Knowing that especially Gram-negative bacterial and fungal infections are a major cause of morbidity and mortality following OLT [2], we used selective bowel decontamination (SBD) as described by Stoutenbeek et al. [7]. With SBD we eliminated the endogenous source of Gram-negative bacteria and *Candida* to prevent infections with these pathogens [6]. SBD consisted of the nonabsorbable antibiotics polymyxin B, tobramycin and nystatin as suspension administered via the oropharynx and gastrointestinal tract four times per day. Prophylactic perioperative systemic antibiotic coverage with cefotaxime, tobramycin and metronidazole was added for 48 h. All patients received anti-CMV immunglobulin on day 1 and 14. Acyclovir was given in prophylactic dosage (800 mg/day) for 8 weeks post-transplant. Infections were diagnosed according to criteria proposed by Wiesner et al. [8].

Results

The 1-year survival in both groups was over 90% (ATG 90.8%, BT 563 90.9%). In the ATG group, two patients died from fulminant relapsing hepatitis B after 7 and 8 months, two patients died at 3 and 6 weeks from systemic mycosis, one patient died 11 months after OLT from tumour recurrence and one patient from chronic rejection. In the BT 563 group there were three deaths. One from acute heart failure 11 days after OLT, one from tumour recurrence and one from chronic rejection 6 months after transplantation.

No clinical side effects were noted during the BT 563 treatment period. In the ATG group 24 significant infections were seen in the first 4 weeks after OLT (Table 1). Due to SBD the majority of 21 bacterial infections were related to Gram-positive organisms. Among them were

Table 1. Early infections after OLT under ATG ($n = 70$)

Pathogen	n[a]	Site	Organism (n)
Bacteria			
Gram-negative	2	Urinary tract (2)	*Pseudomonas* (1)
Gram-positive	19	Wound infection (4)	*Proteus* (1)
			Streptococcus group D (2)
		Urinary tract (3)	*Nocardien* (1)
		Cholangitis (10)	*Staphylococcus aureus* (1)
		Septicaemia (2)	*Streptococcus* group D (3)
			Streptococcus group D (8)
			Streptococcus viridans (1)
			Staphylococcus coag.-neg. (1)
			Staphylococcus aureus (1)
			Streptococcus viridans (1)
Fungi	3	Septicaemia (2)	*Mucor* (1)
		Pneumonia (1)	*Aspergillus* (1)
			Candida albicans (1)

[a] A total of 24 infections were suffered by 19 patients

Table 2. Early infections after OLT under BT 563 ($n = 33$)

Pathogen	n[a]	Site	Organism *(n)*
Bacteria			
Gram-negative	1	Septicaemia (1)	*Escherichia coli* (1)
Gram-positive	4	Cholangitis (2)	*Streptococcus* group D (2)
		Urinary tract (1)	*Streptococcus* group D (1)
		Wound infection (1)	*Staphylococcus aureus* (1)
Virus	1	Pneumonia (1)	CMV

[a] A total of six infections were suffered by five patients

Table 3. Incidence of early infections (≤ 28 days)

	ATG	BT 563
Bacterial	21/70 (30%)	5/33 (15.2%)
Viral	0/70 (0%)	1/33 (3.0%)
Fungal	3/70 (4.2%)	0/33 (0%)
Total	24/70 (34.3%)	6/33 (18.2%)

Table 4. Incidence of early rejection (≤ 28 days)

	ATG	BT 563
Incidence	16/70 (22.9%)	3/33 (9.1%)
steroid sensitive	12	2
with response to OKT3	4	1

ten episodes of cholangitis, two bacteraemias, four wound infections and three infections of the urinary tract. There were only two infections of the urinary tract caused by Gram-negative bacteria. In three patients fungal infections were seen. The two patients with fungal septicaemia died 3 and 6 weeks after OLT.

In the BT 563 group, five patients had six infections (Table 2). Five of these infections were caused by bacteria (two cholangitis, one wound infection, one infection of the urinary tract and one septicaemia). One patient developed severe CMV pneumonia after transplantation. He had to be treated with gancyclovir and anti-CMV immunoglobulin for 39 days and also needed respirator treatment for 14 days. However all infections in the BT 563 group responded to antibiotic therapy.

Observing the incidence of early infections (Table 3) there was a clear difference between the two groups. A higher overall incidence of infection was seen in the ATG group. While two early fatalities due to fungal infections were observed in the ATG group, no infection-related deaths occurred in the BT 563 group.

Discussion

These first results indicate a lower incidence of early infectious complications when ATG is replaced by the new monoclonal IL-2R antibody BT 563 as part of the quadruple immunosuppression after OLT. One possible reason for the observed decrease in early infection was a reduced incidence of early rejection under BT 563 in our experience (Table 4) also described by Otto et al. [5]. Secondly, the monoclonal IL-2R antibody BT 563 inhibits only activated IL-2-dependent T cells, thus resulting in a more specific immunosuppression [4]. In contrast ATG or OKT3 react with all T lymphocytes, thus resulting in a more general immunosuppression, increasing the risk of infection.

Further controlled and prospective studies are necessary to evaluate these observatioans.

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