Summary

Until 1979 in most liver transplantation centres a combination of azathioprine and prednisolone was administered as immunosuppression for rejection prevention. The liver transplant programme in Groningen started with this immunosuppressive regimen as well. Several years later CsA was added to this regimen. In this thesis, the experience with CsA as part of a triple drug immunosuppressive regimen for rejection prevention in liver transplantation is described.

In Chapter 1 the short term results, achieved with conventional immunosuppression, are compared with our initial experience with CsA based triple immunosuppression. The major conclusion was, that the one-week liver biopsy under CsA based triple therapy showed a normal histology. This was a major improvement, since ninety percent of the biopsies taken under conventional immunosuppression showed acute rejection. Additionally, a year after liver transplantation liver histology was normal in most biopsies under CsA based triple therapy. This was also in contrast to most liver biopsies of patients treated with conventional immunosuppression. Moreover, the liver tests and the graft- and patient survival were better in the patients treated with CsA based immunosuppression. Thus the immediately visible advantage of CsA remained present, even after a longer period of time.

In Chapter 2 the consequences of a histological proven acute rejection, diagnosed in the one-week liver biopsy are discussed.

Over the years it became clear, observing the clinical course of rejection, that not every episode of early acute rejection required treatment. We, therefore, retrospectively studied a group of patients with a histologically diagnosed grade I acute rejection. Two-thirds of the these grade I rejection episodes did not require treatment with extra methylprednisolone. This led to a major reduction of the necessary dose of corticosteroids. The increase of all liver tests, except APh, between day 5 and 7 proved to be important parameters for the decision which rejection episode needed treatment and which did not. The difference in the clinical and biochemical presentation between the treated and untreated grade I rejection episodes indicated on the one hand a histologic similarity, but on the other hand a functional difference of the inflammatory cells in the portal triangles. Follow-up demonstrated, that selectively withholding treatment of early rejection in this study group did not result in an increase of the incidence of acute rejection episodes later after transplantation. Neither the liver histology of later obtained biopsies nor the occurrence of infection episodes differed between the treated and untreated patient groups.

In Chapter 3 a study concerning the absorption of CsA under various circumstances is described. Intravenous administration of CsA resulted in a rapid increase of the serum concentration level with a distinct and early peak. For the absorption of orally administered CsA, the presence of bile is necessary. Early after transplantation the bile is deviated from the gastrointestinal tract through an external drain.
which has been positioned in the choledochal duct. Because only a small part of the
total bile production will pass along this drain, some absorption is still possible.
Compared with the intravenous curve the absorption with open drain was strongly
diminished. Clamping of the biliary drain resulted in a much improved absorption.
however, the peak concentration remained lower and was reached later, compared
with the intravenous absorption. Basing ourselves on these observations, the daily
bile production is re-administered to the patient through a percutaneous feeding
jejunostomy, together with tube feeding.

CsA has had a major impact on the development of solid organ transplantation.
Regrettfully, few medicaments are selective in such a way, that side-effects are
absent. CsA is no exception to this rule. The number of side-effects is considerable
and especially the long-term nephrotoxicity is a point of concern. Consequently it
was decided to study the possibility and consequences of CsA withdrawal from the
triple drug immunosuppressive regimen.

In Chapter 4 the influence of CsA withdrawal on the renal function is described.
The renal function was determined, by measuring the GFR and ERPF. These
measurements were performed on two occasions, i.e. once during CsA therapy,
and the second time half a year after the discontinuation of CsA therapy. Six
months after the discontinuation of CsA administration the renal function had
significantly improved. Normal values were not obtained however. To determine
the maximal renal function and the possible recovery after discontinuation of CsA,
the kidneys were stimulated during both measurements with dopamine, amino-acids
and a combination of both. After more than two years of CsA treatment, dopamine
stimulation under CsA containing immunosuppression increased the ERPF with
42%. This observation could lead to the conclusion, that the influence of dopamine
stimulation on the renal function is predictive for the degree of renal improvement
after CsA withdrawal. This finding also shows, that after two years of CsA
treatment there still is renal reserve capacity.

In Chapter 5 the biochemical and histological consequences of CsA withdrawal are
described. It became clear that, because of CsA withdrawal, biochemical and
histological abnormalities appeared. But, nevertheless CsA could be permanently
withdrawn from the immunosuppressive regimen for seven out of the ten investi-
gated patients. After CsA withdrawal the liver histology also improved on the long
term. This study showed that it must be possible to discontinue CsA therapy in the
long run after transplantation in the majority of the patients. If this is possible with
fewer consequences later after transplantation, has yet to be established.

In Chapter 6 the advantages and disadvantages of the current CsA based triple
immunosuppressive regimen are described. This immunosuppressive regimen
results nowadays in survival figures of up to 90%. Therefore, the gain in terms of
graft- and patient survival achieved with stronger immunosuppression will be
limited. This is in contrast with the situation that existed with the introduction of
CsA. As was described in the previous chapters CsA also has disadvantageous,
toxic side-effects. If a reduction of toxic side-effects could be achieved by combi-
ning new and old medicaments, this would mean a major improvement. Based on the currently available literature data, Chapter 6 describes the characteristics of the immunosuppressive drugs, which now are under investigation in phase I and phase II trials. Though the results of the newly developed drugs look promising so far, single drug therapy does not seem to be an option. Also in the future, combination therapy will remain necessary to keep drug toxicity as low as possible. A major option is a combination scheme with CsA or FK506. A combination of three or more drugs will reduce the necessary dose of each individual drug, thus diminishing the dose related side-effects. If, after all, side-effects still induce the discontinuation of a certain drug, then the larger number of newly developed drugs also offers the opportunity of choosing alternative immunosuppressive therapy.

A combination of old and newly developed drugs might ultimately improve the liver transplant results. It may also lead to an improvement of the quality of life of the transplant patient.