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ORIGINAL ARTICLE

Systemic mycophenolate mofetil avoids immune reactions in penetrating high-risk keratoplasty: preliminary results of an ongoing prospectively randomized multicentre study*

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Summary

Recently, in a monocentre study mycophenolate mofetil (MMF) was demonstrated to be efficacious and safe in penetrating high-risk keratoplasty. Here, preliminary results of a randomized multicentre trial are presented. To date, 86 of 140 scheduled patients undergoing high-risk penetrating keratoplasty have already been randomized into the two study groups: 48 into the MMF group and 38 into the control group. All 86 patients received fluocortolon 1 mg/kg body weight/day, tapered within 3 weeks, and topical prednisolone acetate 1% tapered within 5 months. MMF was administered at a daily oral dose of 2×1000 mg for the first 6 postoperative months. Thereafter, MMF was tapered within 2 weeks. The proportion of grafts with immune reactions and side-effects were the main outcome measures. Within an average follow up of 9.2 ± 6.6 months two patients developed reversible endothelial immune reactions in the MMF group after cessation of MMF application. In the control group, five reversible and three irreversible immune reactions were observed within an average follow up of 10.1 ± 7.6 months. According to Kaplan and Meier analysis, the ratio of grafts without immune reactions was estimated 89% 1 year postoperatively in the MMF group, in contrast to only 67% in the control group ($P = 0.03$; log-rank test). Fifteen patients experienced side-effects, especially gastroenterotoxicity, tachycardia, arthralgia or systemic infections. All attributable side-effects were reversible. Systemic MMF may be an effective and safe immune modulating drug in the prophylaxis of immune reactions after penetrating high-risk keratoplasty.

Introduction

Mycophenolate mofetil (MMF), the morpholinoethylester of mycophenolenic acid (MPA), is a potent inhibitor of inosine monophosphate dehydrogenase. MPA inhibits the proliferation of T- and B-lymphocytes [1]. The efficacy and safety of MMF in a daily oral dose of 2×1000 mg combined with cyclosporin A (CsA) and corticosteroids have been shown after kidney transplantation [2–4]. The same is true for daily doses of 3000 mg after heart and liver transplantation [5,6].

In pro- and retro-spective monocentre studies short-term application of systemic CsA was shown to improve graft prognosis in patients undergoing high-risk penetrating keratoplasty [7–9]. Side-effects like nephrotoxicity, hepatotoxicity or arterial hypertension, however, occur in

up to 41% of patients treated with CsA as systemic mono-immunomodulation over 6–12 months postoperatively [9–11]. CsA blood trough levels should not exceed 150 ng/ml in order to minimize the risk of side-effects. Expensive laboratory monitoring is necessary. Therefore, alternative effective and safe immunomodulative drugs for penetrating high-risk keratoplasty are desirable.

After penetrating keratoplasty, the efficacy of MMF was demonstrated in the rat model [12,13]. In a prospectively randomized monocentre study, MMF was shown to be an effective and safe potential alternative therapeutic option to CsA after penetrating high-risk keratoplasty [10,11]. That study, however, did not include a control group without systemic immunomodulation.

A prospectively randomized multicentre study, therefore, was conducted in which patients receiving MMF over 6 months postoperatively are being compared with a control group without midterm systemic immunoprophylaxis. In this study, we want to find out if MMF is able to reduce the proportion of grafts with immune reactions.

Methods

Patient selection, treatment and follow up

A total of 140 high-risk patients are scheduled for the study. A first evaluation was planned after recruitment of about two-third of the total number of patients. To date, 86 patients have been recruited and randomized into the two study groups: 48 into the MMF group and 38 into the control group (Table 1). All patients gave written informed consent after obtaining approval by the local ethics committees of all participating centres. The study was performed in accordance to the Declaration of Helsinki. High risk was defined by the presence of deep vascularization in three or four quadrants, a history of previous keratoplasty, position of the graft close to the limbus (<1 mm), severe atopic dermatitis (associated with atopic keratoconjunctivitis) or steroid response glaucoma (Table 2). Steroid response glaucoma was regarded a high-risk situation as no systemic or topical steroids can be administered postoperatively. The incidence of immunological events is known to increase in such situations [14,15].

Table 1. Recipient data (chi-square test*, *t*-test**).

	MMF group	Control group	*P*-value
Mean age (years)	59 ± 17 (25–87)	57 ± 17 (21–84)	0.76**
Gender, *n* (male/female)	28/20	20/18	0.37*
Previous surgical procedures, *n* (keratoplasty/cataract surgery/glaucoma surgery)	40/20/7	24/9/1	0.42*
Follow up (months)	9.2 ± 7.4 (0.26–24)	10.1 ± 7.6 (0.26–24)	0.86**
Graft diameter ($n < 8.0/n \geq 8.0$)	38/10	22/16	0.58*

MMF, mycophenolate mofetil.

Table 2. Indications for surgery (chi-square test, $P = 0.2$).

	MMF group	Control group	Total
Re-keratoplasty (*n*)	40	24	64
Steroid-induced glaucoma (*n*)	1	1	2
Deep vascularization in three to four quadrants (*n*)	1	2	3
Severe atopic dermatitis (*n*)	2	3	5
Graft position close to limbus (*n*)	4	8	12

MMF, mycophenolate mofetil.

Patients with a history of malignant tumours, with acute or chronic systemic infections, acute peptic ulcer disease, pregnancy or insufficient contraceptive measures were as well excluded as patients younger than 18 years. Herpetic eye disease or other acute corneal infections were further exclusion criteria. Herpetic eye disease was regarded as an exclusion criterion because it may be clinically impossible to differ between immune reactions and intraocular herpes recurrences postoperatively in some patients. Furthermore, herpes recurrences may trigger endothelial immune reactions.

All patients had physical and laboratory examination prior to surgery.

The 86 patients were randomized to receive systemic MMF (48 patients) or no midterm systemic immunoprophylaxis (38 patients). Randomization was performed for all study centres in Düsseldorf using a box with 140 leaflets (70 for the MMF group and further 70 for the control group). MMF was administered orally in a daily oral dose of 2×1000 mg over 6 months postoperatively (this dose is standard after renal transplantation). Thereafter, 2×500 mg were administered for 2 weeks, and then systemic immunosuppression was stopped. Additionally, all patients except those with steroid-induced glaucoma received systemic (1 mg/kg body weight fluocortolone, tapered within 3 weeks postoperatively) and topical corticosteroids (starting with five drops prednisolone acetate 1% daily after epithelial consolidation, tapered within 5 months). The use of fluocortolone at the above-mentioned dose has been standard in many of the participating centres for many years. In this study, fluocortolone was administered in order to minimize the risk of postoperative intraocular inflammation. This may be important regarding immunological complications or endothelial cell loss.

Postoperatively, all patients were monitored for efficacy (clear graft survival, immune reactions, endothelial cell loss) and side-effects of the drug (e.g. gastroenterotoxicity). We did not use a scoring system to monitor efficacy. Grafts were regarded clear if opacities could not be detected in any of the corneal layers regarding the central 3 mm. Immune reactions were diagnosed according to the below mentioned criteria.

Postoperative controls were scheduled daily in the first week and after 2, 3, 6, 9, 12, 18 and 24 months. At every control, evaluation of visual acuity, slitlamp examination and estimation of intraocular pressure were performed. Specular microscopy of the graft and examination of the retina were done after 2, 3, 6, 9, 12, 18 and 24 months. Furthermore, the patients were questioned regarding possible side-effects using a standard list of questions. Finally, physical examination and blood controls were done. In between the patients were closely examined by general practitioners and ophthalmologists outside the clinic. Additional ophthalmological treatment (e.g. glaucoma medication) had to be arranged in cooperation with the clinical centres.

Mostly, surgery was performed using grafts preserved in organ culture with an endothelial cell density of at least 2000 cells/mm^2. Of 23 cases in each study group the human leucocyte antigen (HLA)-types of donor and recipient could be determined, in the remaining cases HLA-typing of the donor failed. HLA-typing was performed using serological tests for class I and molecular genetic methods for class II. There was no statistically significant difference between the two groups for HLA-mismatches (chi-square test, $P > 0.05$).

A 10.0 nylon double running cross-stitch suture was used for graft fixation, and, if necessary, in case of lens opacification, cataract surgery was performed simultaneously. This was the case in six patients in the MMF group and in two patients in the control group. Postoperatively, immune reactions were diagnosed by endothelial precipitates adhering to graft endothelium with (severe endothelial immune reactions) or without (mild endothelial immune reactions) stromal oedema or by the presence of noninfectious stromal infiltration (subepithelial infiltrates = stromal immune reactions) [16,17]. These patients were treated with prednisolone acetate 1% eye drops hourly and, in severe cases, additionally with 1 mg/kg body weight fluocortolone.

Endothelial cell loss was assessed only in patients with at least three postoperative endothelial cell density values. Patients with endothelial immune reactions were excluded from this calculation. The individual mean loss of endothelial cells per year was derived from the postoperatively acquired endothelial values of each patient individually. This was done by calculating the slope of the regression line for each scatterplot of logarithmized endothelial cell density values plotted against time [18,19].

Statistical methods

Treatment groups were compared using the *t*-test for independent samples (patient age, follow up, donor age, period between donor's death and graft preparation, organ culture period, preoperative endothelial cell density, postoperative endothelial cell loss) or chi-square test (patient gender, previous surgical procedures, indication for surgery, graft diameter, donor gender, organ culture/short-term culture, HLA-data, distribution of side-effects). Efficacy parameters were clear graft survival and occurrence of clinically detectable immune reactions. Calculation was done using the Kaplan–Meier estimator [20], evaluation for statistical significance via log-rank test. A *P*-value below 0.05 was regarded statistically significant. Seventeen of 48 patients in the MMF group and 14 of 38 patients in the control group had a follow up of <6 months, i.e. in the MMF group 17 patients still received systemic immunomodulation at the time of analysis. Twenty-three patients in the MMF group and 19 patients in the control group had a follow up of <12 months.

All statistical evaluation was performed using SPSS Windows NT 4.0 (Microsoft Corp., Redmond, USA).

Results

Demography

To date, 86 patients have given written informed consent. Of these 48 were randomized into the MMF group and 38 into the control group (Fig. 1). None of the patients was lost for follow up.

There was no statistically significant difference between the two study groups considering patient age, patient gender, previous surgical procedures, follow up, graft diameter, indication for surgery, donor age, period between donor's death and graft preparation, donor gender, organ culture/short-term culture, organ culture period, preoperative endothelial cell density and HLA-data (Tables 1 and 2).

Efficacy

Within an average follow up of 9.2 ± 6.6 months two patients of the MMF group developed reversible endothelial immune reactions after cessation of MMF application (one patient immediately after having stopped MMF prophylaxis, i.e. 6.5 months after surgery, the other 1 year after surgery). In the control group five reversible and three irreversible endothelial immune reactions were observed within an average follow up of

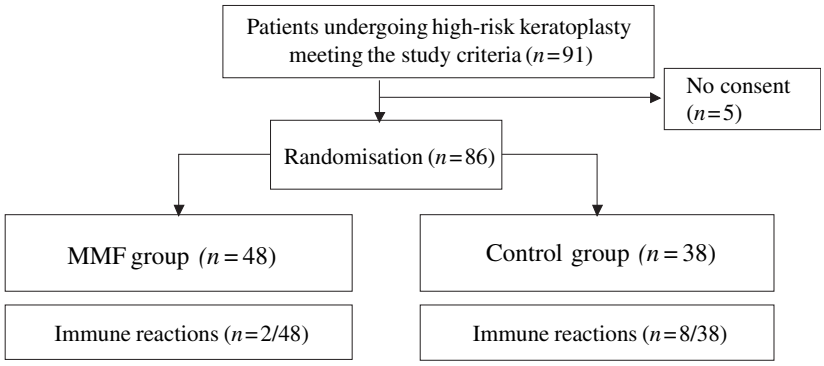

Figure 1 Consort scheme of the study.

10.1 ± 7.6 months. According to Kaplan and Meier, the ratio of grafts without immune reactions was estimated 89% 1 year postoperatively in the MMF group, in contrast to only 67% in the control group (Fig. 2, $P = 0.03$; log-rank test).

In the MMF group no patient experienced irreversible graft failure, in contrast to three patients in the control group (irreversible endothelial immune reactions).

Endothelial cell loss was similar in both study groups. In the MMF group (22 patients with three or more endothelial cell density values) 9.0% of endothelial cells were lost per year in comparison with 8.2% in the control group (16 patients with three or more endothelial cell density values; *t*-test; $P = 0.86$). The number of patients with at least three postoperative cell density values was limited due to technical difficulties in obtaining specular microscopic photographs.

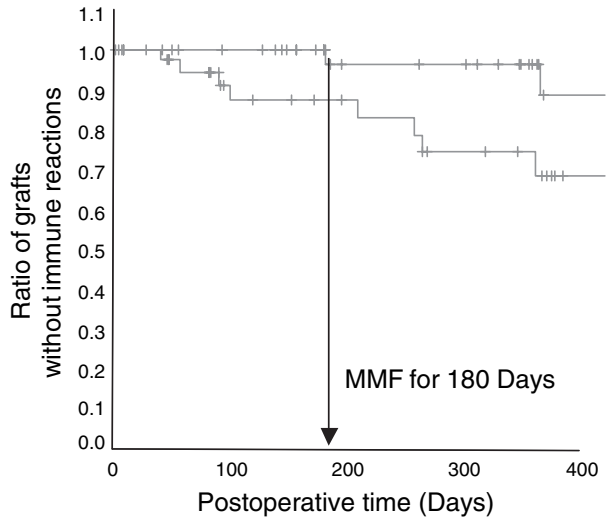

Figure 2 Patients with mycophenolate mofetil (MMF) experience less immune reactions; Kaplan–Meier curves (log-rank test, $P = 0.03$).

Safety

Fifteen patients of the MMF group experienced side-effects (Table 3). The side-effects occurred after an average treatment period of 2 (0.1–6) months. In all patients with infections (two patients with bronchitis, one patient with pneumonia) and in both tumour patients (73 and 63 years, respectively) systemic immunosuppression was continued and the patients were not excluded from the study. The infections were reversible using systemic antibiotics. The tumour patients were picked up due to close internal and laboratory controls in the follow-up period.

Four of 48 patients were excluded from the MMF group because of premature withdrawal of the drug. In two of these four patients compliance problems occurred, in one patient with a history of gastroenterotoxicity deterioration was reported (premature withdrawal of the drug 1 week postoperatively) and one further patient experienced asthma (premature withdrawal of the drug 5 months postoperatively). The latter two patients are included in the 15 patients with side-effects mentioned above. Regarding one additional patient who was excluded due to a dose reduction of MMF (see below) 43 were left for evaluation of efficacy.

Two of 38 patients were excluded from the control group within the follow-up period (both patients because of compliance problems), i.e. 36 were left for evaluation.

Table 3. Side-effects of mycophenolate mofetil (15 patients).

	n	%
Gastroenterotoxicity	8	16.6
Tachycardia	4	8.3
Arthralgia	3	6.3
Systemic infections	3	6.3
Malignant tumours	2	4.2
Asthma	1	2.1

In only one of the 13 of 15 patients with side-effects but without premature withdrawal of MMF the dose was reduced. This patient had a history of heartburn and experienced a deterioration within the first 2 months after keratoplasty. The daily MMF dose was reduced to 2×500 mg and maintained. Heartburn disappeared under the reduced dose. The graft did not experience an immune reaction or other complications in the follow-up period.

Discussion

The immune privilege of the cornea and the anterior chamber is responsible for the excellent prognosis of the graft after penetrating normal-risk keratoplasty, e.g. in keratoconus, Fuchs' endothelial dystrophy or avascular nonherpetic scars [21]. Without systemic immunosuppression more than 90% of HLA-untyped grafts remain clear within the first 2 postoperative years in patients with, e.g. keratoconus [22–24]. The situation is completely different if the recipient's cornea is vascularized, if the recipient has a history of previous keratoplasty or if a graft is positioned close to the limbus. The Collaborative Corneal Transplantation Studies Group reports that 62% of high-risk grafts experience at least one immune reaction [25]. Hill even observed up to 75% immunological graft failures in such situations [7,8].

Systemic MMF was suggested to be effective in patients with uveitis [26,27] and penetrating keratoplasty [10,11]. Larkin and Lightman treated 11 patients with uveitis. Ten of these showed a favourable response to MMF [26]. Baltatzis *et al.* applied systemic MMF in 54 patients with various inflammatory chronic ocular disorders, mainly with uveitis [27]. An improvement was noted in 51 of these patients [27].

Here, an ongoing prospectively randomized multicentre study is conducted in which patients receiving MMF over 6.5 months postoperatively are compared with a control group without midterm systemic immunoprophylaxis. The application period of 6.5 months was (almost) identical with that of previous studies examining the effect of systemic CsA in the prophylaxis of immune reactions after penetrating keratoplasty [9–11]. In the past we had the impression that such a limited period of prophylaxis might induce midterm or even long-term tolerance and that it might reduce the risk of (irreversible) side-effects. In this study, 89% of the grafts in the MMF group and 67% of the grafts in the control group did not experience immune reactions. Despite limited follow up and despite recruitment of up to now only 86 of 140 patients scheduled for the study this difference is already statistically significant. No immune reaction was observed in the MMF group as long as MMF was administered. Only after cessation of the drug two patients experienced reversible endothelial immune reactions. In these two patients induced immune tolerance must have been incomplete, but possibly strong enough to avoid irreversible immune reactions. The question arises how to identify patients with incomplete immune tolerance in time in order to perform systemic immunosuppression in the long run, i.e. much longer than 6 months as in this study. Possibly, some patients need systemic prophylaxis in the long run, i.e. for many years. Determination of cytokine levels in the anterior chamber may be a first step towards the development of 'predictive parameters' [28].

Main side-effects in the MMF group were gastrointestinal disorders, tachycardia, arthralgia and systemic infections. These side-effects were reversible and mostly well-tolerated by the patients. Two patients experienced malignant tumours, 2 and 3 months, respectively, after entering the study. Because of this short period of time it is not likely that MMF was causative. Most probably, these tumours pre-existed and were detected in an early stage because of intensive internal controls in the study.

Larkin and Lightman observed in the above-mentioned uveitis study in only one of 11 patients side-effects (nausea and headaches) [26]. The variety of side-effects observed by Baltatzis *et al.* in the other above-mentioned much larger uveitis study was similar to the side-effects detected in the present study [27].

In both uveitis studies the same MMF dose was applied as in our study, in the study of Larkin and Lightman over 4–9 months [26], in the study of Baltatzis *et al.* over a mean period of 7 months that is similar to that of our study [27].

In conclusion, in this ongoing prospectively randomized multicentre trial systemic MMF in a daily oral dose of 2×1000 mg was shown to considerably reduce the proportion of immune reactions. All attributable side-effects were reversible. Therefore, systemic MMF may be an effective and safe armament in the prophylaxis of immune reactions after penetrating high-risk keratoplasty. Longer follow up, however, is necessary to state if the protective effect is long lasting.

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Further participating centres: Eye Hospital, University Clinic Munich, Munich, Germany; Eye Clinic, St Franziskus Hospital, Münster, Germany; Eye Hospital, University Clinic Halle, Halle, Germany; Eye Hospital, University Clinic Homburg/Saar, Homburg/Saar, Germany; Eye Hospital, University Clinic Essen, Essen, Germany.

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