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Evaluation of Mycophenolate Mofetil role as an immunomodulator in high risk keratoplasty patients

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Short title: Mycophenolate Mofetil role as an immunomodulator in high risk keratoplasty patients

Abstract:

Background: High risk keratoplasty had higher rates of immune graft rejection than low risk keratoplasty due to the alteration of corneal immune privilege. Immunomodulatory therapy in the form of Mycophenolate Mofetil (MMF) had shown a significant decrease in immune graft rejection rates.

Objectives: This study was conducted to evaluate the role of Mycophenolate Mofetil in reduction of corneal graft rejection rates in high risk keratoplasty patients.

Patients and Methods: Study included 50 eyes scheduled for penetrating keratoplasty who met the inclusion criteria of high risk keratoplasty. Patients will be randomly divided into two groups; MMF group (25 patients) received MMF as an immunosuppressive drug pre and postoperative in addition to the topical steroid and antibiotic eye drops postoperative. Corticosteroid group (25 patients) received systemic corticosteroid pre and postoperative in addition to topical steroid and antibiotic eye drops postoperative.

Results: Statistically significant differences were recorded in terms of BCVA after 1st week, 1st month, 3rd month, 6th month and one year of follow up in each group of studied groups. Statistically significant differences were documented according to complications of treatment after keratoplasty, state of corneal grafts and number of rejection episodes between studied groups (P<0.001).

Conclusion: Mycophenolate Mofetil has a significant role in decreasing rates of corneal graft rejection after high-risk penetrating keratoplasty.

Keywords: High risk penetrating keratoplasty, corneal graft rejection, Mycophenolate Mofetil.

INTRODUCTION:

Keratoplasty is the most common procedure of organ/tissue transplantation which has high success rates when done in non-vascularized and non-inflamed (low risk) host beds[1]. Corneal grafting doesn't often require systemic immunosuppression in contrast to other allogeneic organ/tissue transplantation forms because of the cornea's immune privilege feature. Although there are high long-term success rates with low-risk keratoplasty, 30–60% high-risk penetrating keratoplasty grafts have rejection episodes and 70% fail within 10 years[2].

Ocular disorders that have high rates of corneal transplant rejection include eyes with corneal neovascularization in two or more quadrants, Herpes simplex keratitis (HSK), uveitis, silicone oil keratopathy, infection and anterior iris synechiae[3]. Other factors that increase the probability of graft rejection include young recipient age, previously failed or rejected grafts, previous surgeries including glaucoma and recipient graft trephination of more than 8.25 mm[4]. Despite breakthroughs in

anti-inflammatory medications, glaucoma control, surgical techniques and postoperative care, this patient group continues to have substantial rejection rates (may reach 60%)[5].

The leading cause for graft failure following full thickness penetrating keratoplasty is still immune rejection. Consequently, guidelines for managing and preventing rejection are essential to a corneal allograft's survival[6].

The most common medication prescribed to prevent rejection after keratoplasty is topical corticosteroids, but there are significant variations in postoperative management protocols[7]. Although weaker steroids have little side effects, some patients may require the strongest available type of corticosteroids to control inflammation. The most widely prescribed topical corticosteroid is prednisolone acetate 1%[8].

Different steroid sparing agents have been discussed in different studies in management of high risk keratoplasty. For example, Cyclosporin (CsA), Tacrolimus, Sirolimus and Mycophenolate mofetil (MMF)[9]. Due to a number of serious side effects, CsA administration is restricted[10]. MMF, a reliable and effective immunosuppressive drug, showed less side effects than CsA so that MMF became a safe choice in high risk keratoplasty management[11].

A number of studies have been published to report the efficacy of these immunosuppressive agents as prophylaxis against corneal graft rejection. However, the results have been inconsistent and there is lack of evidence-based guidelines about the use of these agents for immunoprophylaxis in high-risk corneal transplantation[12].

MMF is the pro-drug of the active substance mycophenolic acid [MPA], which selectively inhibit T and B-cell proliferation through inhibition of the de novo synthesis of guanosine nucleotides. Infections, gastrointestinal disturbances, anemia, leucopenia, hyperlipidemia and arterial hypertension are the most common side effects of MMF. All of which are reversible after discontinuation of the drug's dosage[13].

An initial dose of MMF was prescribed two weeks before high risk keratoplasty of 2×500 mg daily which is increased to 2×1000 mg daily for one month after the procedure. After the first month of procedure, MMF was tapered to 2× 500 mg daily, then it is tapered to 2×250 mg daily after six months and finally it is discontinued after one year of surgery[14]. MMF is rapidly metabolized to mycophenolic acid [MPA] in the liver when administered orally. A bioavailability of 94% is achieved with oral administration[15].

PATIENTS AND METHODS:

This was a prospective interventional randomized study conducted on a total of 50 eyes who met the inclusion criteria of high risk keratoplasty. The study was approved by Institutional Research Board (IRB) (MS.20.10.1277), Faculty of Medicine, Mansoura University.

Inclusion criteria

Patients with previously rejected grafts, corneal neo-vascularization in two or more quadrants, keratitis after being inactive for at least 6 months, ocular surface disease, fellow eye had penetrating keratoplasty and children less than 16 years old are considered high risk criteria which lead to higher rates of immune graft rejection. Immune graft rejection rates significantly decreased with immunomodulatory therapy in the form of Mycophenolate mofetil.

Exclusion criteria

Immunocompromised patients, straight forward keratoplasty (keratoconus) and lamellar keratoplasty were excluded from study.

Preoperative:

Medical and ocular history were taken for all patients. Assessment of best corrected visual acuity (BCVA) for all patients by Landolt C chart then converted into LogMAR for statistical purpose. Thorough preoperative ocular examination was done to all patients by slit lamp to assess corneal signs with special attention to corneal opacity and neo-vascularization. Preoperative investigations were done for all patients. These investigations were ultrasound b scan, visual evoked potential (VEP), electroretinogram (ERG) to assess retinal functions and anterior segment optical coherence tomography (ASOCT) to assess the depth of corneal opacity.

Preoperative immunosuppressive therapy:

Group 1 [MMF]: patients received MMF 2 weeks before operation 500 mg orally twice daily then increased up to 2000

mg daily in divided doses for 6 months then reduced to 1000 mg daily in divided doses for 6 months according to follow up assessment in addition to topical regimen which consisted of prednisolone acetate 1% 5 times a day then it was tapered according to clinical assessment, antibiotic drops after surgery 3 times daily for 2 weeks and tear substitutes 4 times daily.

Group 2 [Corticosteroid]: patients received systemic prednisolone 1 mg/kg/day one week before operation tapered over 2 weeks and topical prednisolone acetate 1% 5 times a day tapered over 5 months according to follow up assessment, antibiotic drops after surgery 3 times daily for 2 weeks and tear substitutes 4 times daily.

- **Operative: (penetrating keratoplasty)** The center of the host cornea was marked with a senskey hook, calipers were used to measure the corneal diameter to determine the appropriate size for donor trephine. Donor tissue was punched, typically aiming for 0.25 or 0.5 mm larger than the planned host trephination. Paracentesis was created in the anterior chamber then healon was injected into the AC to preserve its depth and stability. After using a blade to enter the AC, host corneal tissue was resected using curved corneal scissors. Donor graft was secured to the host corneal tissue using interrupted 10-0 nylon sutures. Sixteen interrupted sutures were applied. Sutures were rotated to bury the knots; astigmatism was assessed using an intraoperative keratometer and additional sutures were considered to reduce astigmatic error. Soft contact lens was applied.
- **Postoperative:** Follow up of BCVA with complete ophthalmic examination with 1-week interval in the first month after the procedure then 1-month interval in the following 6 months then 2-months interval in the following 5 months. Monitoring signs of immunological graft rejection for all patients. Monitoring side effects of MMF every month with an internal medicine consultation by CBC, liver and kidney function testing.

Clinical diagnosis of corneal graft rejection:

1. Progressive diminution of vision due to sudden corneal edema extending to deeper layers.
2. Conjunctival and ciliary injection.
3. Infiltrates extending to graft host junction.
4. Neo-vascularization of the graft.
5. Five possible changes are found by clinical specular microscopy during acute rejection episodes: [1] 'blackout' areas caused by wandering cells deposition on the endothelial layer; [2] 'blackout' areas within the cytoplasm of unknown origin; [3] intracellular 'bright' oval bodies associated with the cell nucleus; [4] a notable variation in cell size; and [5] a distinct demarcation line of affected endothelial cells in a linear-type rejection. Even in cases of early rejection, these morphologic alterations were obvious.
6. Assessment of endothelial/Descemet's membrane complex thickness and analysis of anterior chamber inflammation by ASOCT.

- **Statistical analysis:** Data analysis was performed by SPSS software, version 25 (SPSS Inc., PASW statistics for windows version 25. Chicago: SPSS Inc.). Qualitative data were described using number and percent. Quantitative data were described using mean ± standard deviation (SD) for normally distributed data after testing normality using Shapiro Wilk test. Significance of the obtained results was judged at the ($\leq$0.05) level.

Chi-Square, Fisher exact test and Monte Carlo tests were used to compare qualitative data between groups as appropriate. Student t test was used to compare 2 independent groups for normally distributed data. Paired t test was used to compare 2 paired readings for normally distributed data.

RESULTS

Our study enrolled 50 eyes who met the inclusion criteria for high-risk penetrating keratoplasty. They were randomly divided into two groups. MMF was prescribed to the 1st one while 2nd group had received systemic corticosteroid in management protocol.

There were no statistically significant differences between studied groups as regard age, gender and laterality. In MMF group, 44% aged more than 40 years, 44% aged from 16 to 40 years and 12% aged less than 16 versus 52% aged more than 40

years and 35% aged from 16 to 40 years, 12% aged less than 16 years in steroid group. Female gender of MMF group is 48% versus 56% in steroid group. Right side affection was detected among 36% of MMF group and 44% in steroid group as demonstrated in table (1).

Table 1: comparison of demographic characteristics between studied groups.

	Group 1 MMF N=25(%)	Group 2 Steroid N=25(%)	Test of significance
Age / years			
<16 y	3(12.0)	3(12.0)	$\chi^{2\ MC=}$0.367
16-40 y	11(44.0)	9(36.0)	P=0.832
>40 y	11(44.0)	13(52.0)	
Gender			
Male	13(52.0)	11(44.0)	$\chi^{2\ =}$0.321
Female	12(48.0)	14(56.0)	P=0.778
Laterality			
Right	9(36.0)	11(44.0)	P=0.773
Left	16(64.0)	14(56.0)	

MC: Monte Carlo test, χ^2 :Chi-square test

Statistically significant increase in BCVA from preoperative to one month (p<0.001), 2 months (p<0.001), 3 months (p=0.002), 6 months (p=0.04) and at last visit (p=0.05) in MMF group as shown in table (2).

Table 2: BCVA change during follow up periods in MMF group.

	Group 1 MMF mean±SD (LogMAR)	Test of significance	% of change
BCVA Preoperative	1.35±0.34		
BCVA at 1 month	1.12±0.24	P<0.001*	17.0%
BCVA at 2 months	1.06±0.40	P<0.001*	21.6%
BCVA at 3 months	1.07±0.49	P=0.002*	20.9%
BCVA at 6 months	1.14±0.67	P=0.04*	15.3%
BCVA at last visit	1.09±0.80	P=0.05*	18.5%

t:Paired t test , *statistically significant

While table (3) illustrates **statistically significant increase** in BCVA postoperative at 1 month (p=0.003), at 2 months (p<0.001) and at 3 months (p=0.007) from preoperative value in steroid group. Clinically there was decrease in BCVA at last visit in comparison with preoperative values.

Table 3: BCVA change during follow up periods in steroid group.

	Group 2 Steroid mean±SD (LogMAR)	Test of significance	% of change
BCVA Preoperative	1.15±0.14		
BCVA at 1 month	1.01±0.24	P=0.003*	11.9%
BCVA at 2 months	0.961±0.17	P<0.001*	23.9%
BCVA at 3 months	1.01±0.28	P=0.007*	27.4%
BCVA at 6 months	1.07±0.39	P=0.197	18.1%
BCVA at last visit	1.27±0.61	P=0.279	23.1%

t:Paired t test , *statistically significant

A **statistically significant difference** was found between studied groups as regard complications. In MMF group, 6 cases have complications (5 cataract & 1 retinal detachment). RD in this patient was due to blunt trauma after 7 months post-operative and then the patient had frequent attempts in retinal surgeries. While 17 cases in steroid group have progression of cataract and 6 cases have glaucoma as shown in (figure 1).

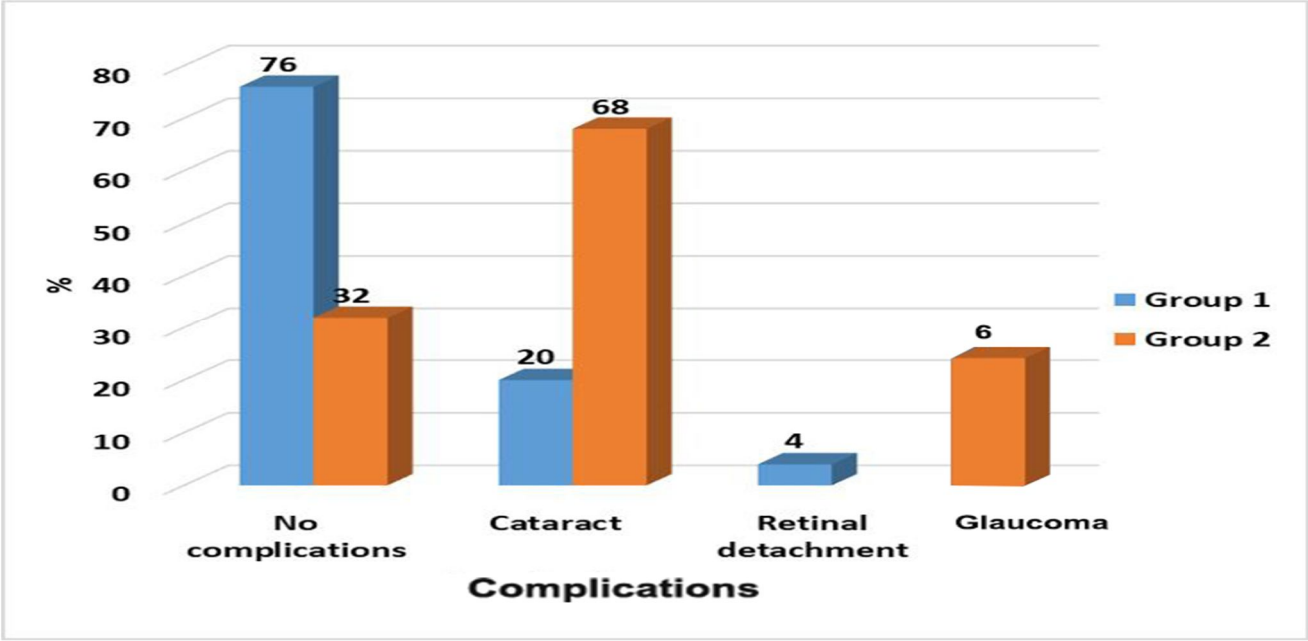

Figure 1. Complications distribution among studied groups

Statistically significant difference was found between studied groups as regard state of corneal graft and shows that 72% of MMF group have clear corneal graft, 16% failure and 12% rejection. The three rejected grafts in MMF group were after one year while the patients had attempts for sutures removal. Among steroid group; 48% rejection and 44% clear corneal graft and 8% failure. Five grafts had rejection after attempts of sutures removal as shown in (figure 2).

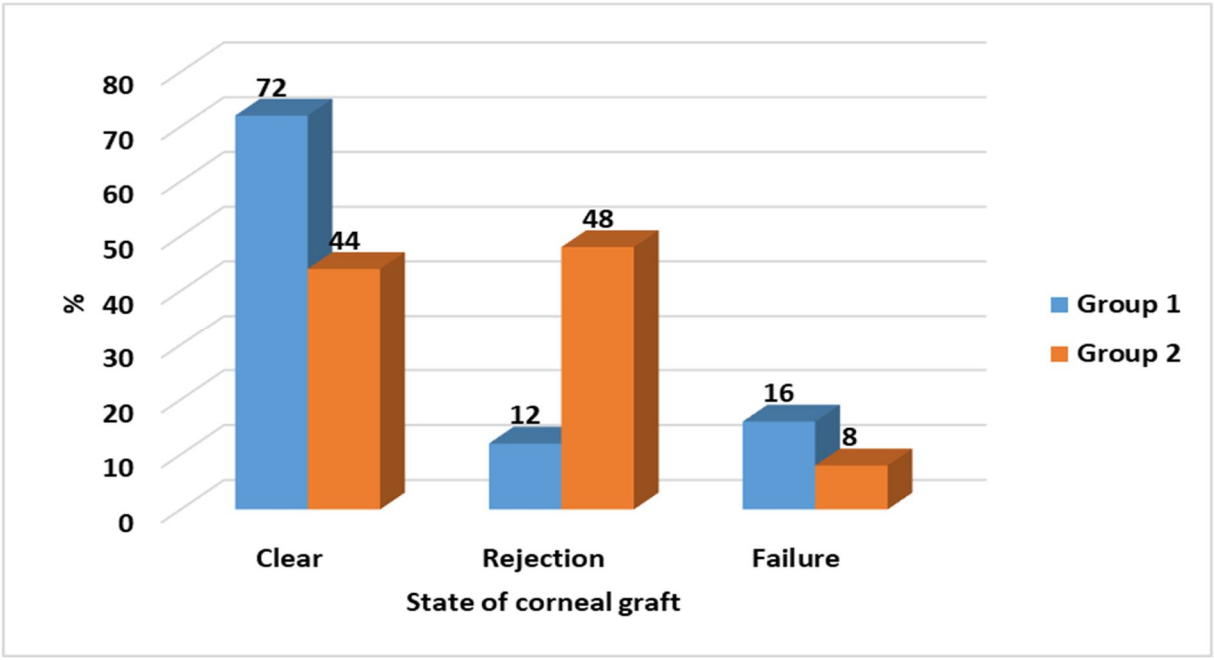

Figure 2. State of corneal graft among studied groups

Table (4) demonstrates that there is a **statistically significant difference** between studied groups in number of cases who experienced graft rejection episodes and whether it was reversible or irreversible. 52% of cases in MMF group had experienced one rejection episode at least, 77% of these cases were reversible. While 64% of cases had experienced one rejection episode at least in steroid group, only 25% of these cases were reversible.

Table 4: number of cases who experienced rejection episodes in studied groups.

Number of cases had rejection episodes	Group 1 MMF N=25(%)	Group 2 Steroid N=25(%)	Test of significance
Total number of cases	13(52.0)	16(64.0)	χ^2=6.89
Reversible	10(77.0)	4(25.0)	P=0.032*
Irreversible	3(23.0)	12(75.0)	

χ^2 :Chi-square test , *statistically significant

DISCUSSION:

Cornea is the most frequently transplanted solid tissue. Compared with solid organ transplantation, corneal transplantation usually yields superior results because of its immune-privileged feature. Low-risk corneal transplant survival rates range from 85% to 90% after ten years[2]. Most low-risk patients respond well to corticosteroid eye drops and do not usually require systemic immunosuppression. Three main factors abolish immune privilege feature of the cornea converting keratoplasty into high-risk procedure. These factors include corneal neo-vascularization in two or more quadrants of corneal opacity which may be superficial or deep stromal new-vessels, inactive keratitis and previous graft rejection. The disturbance of corneal microenvironment that occurs in these conditions is the main cause of corneal allograft rejection which occurs in 40–70% cases/year[16].

In our prospective comparative study that evaluated the use of systemic immunosuppressive therapy in the form of mycophenolate mofetil in comparison of systemic steroid therapy in management of high risk keratoplasty we found no statistically significant differences between the two groups concerning gender, age and laterality.

Female patients in MMF group account for 48% versus 56% in steroid group. Mean age in MMF group is 54.2 and 49.9 in steroid group. Right sided affection was detected among 36% of MMF group and 44% of steroid group.

In a prospective randomized multicentered study demonstrating the comparison between two groups undergoing high risk penetrating keratoplasty. The 1st one includes 57 patients who receive MMF, while the 2nd includes 41 patients who receive systemic steroid therapy, Birnbaum et al, confirmed that there were no statistically significant differences between groups in terms of gender and age. Female patients accounted for 47% in MMF group, and they had the same percentage approximately in steroid group. Mean age of the two groups didn't differ greatly, 58.6±17.0 and 58.3±16.2 in MMF and steroid group respectively[13].

Our study confirmed the improvement in best corrected visual acuity (BCVA) in MMF group in about 16 cases (64%) out of 25 cases from 2 to 0.3 LogMAR, while BCVA in 1 case (0.04%) remained stable in contrast to 8 cases (32%) had worsen BCVA. On other hand BCVA showed an improvement in 11 cases out of 25 (44%) in steroid group, 2 cases (0.08%) had stable BCVA and worsening of BCVA occurred in 12 cases (48%).

According to MMF group there was a statistically significant increase in BCVA postoperative at last visit from preoperative values and from preoperative to one-month, two-month, six-month follow ups and at last visit. BCVA improved from 1.35 to 1.09 LogMAR.

While steroid group showed a statistically significant increase in BCVA at one-month, two-month and three-month follow ups from preoperative value but clinically there was decrease in BCVA in last visit compared with preoperative value which declined from 1.15 to 1.27 LogMAR.

Clinically we found a significant difference between the two groups in concerns of post-operative BCVA, but the difference was not statistically significant. Cause of non-

significance is attributed to the small sample size and short duration of follow up.

The Swedish Corneal Transplant Register for patients undergoing penetrating keratoplasty between 2001 to 2008 for the 2nd time which were considered a high risk keratoplasties because of re-grafting reported that BCVA improvement occurred in a high proportion of patients especially those who had systemic MMF and cyclosporin A as an immunomodulatory agents as, respectively, 86% and 54% of grafts achieved a visual acuity of ≥0.5 at 2 years follow up compared with only 31% of patients who depended on steroid therapy in management of high risk keratoplasty[17].

Few detailed data on the outcomes of visual acuity were reported in high risk keratoplasty studies. In a systematic literature search with subsequent screening of the identified articles that were conducted to obtain potentially eligible randomized clinical trials (RCTs) and comparative cohort studies, four included studies three of them reported the number or proportion of grafts that regained a BCVA ≥ 20/40 (0.3 LogMAR) in the final follow up and only two studies reported the mean visual acuity. Overall, the best results documented with the use of immunomodulatory therapy rather than steroid therapy[18].

According to postoperative complications, 6 patients out of 25 in MMF group had complications. Five patients had progression of cataract, 3 of them underwent cataract surgery. 1 patient had retinal detachment as a result of blunt trauma 7 months postoperative complicated by phthisis bulbi after several attempts of retinal surgeries.

In steroid group we found that 17 patients had progression of cataract, 5 of them had cataract surgery. Six patients had glaucoma, so we considered the incompliance of these patients to steroid drugs that is tapered gradually with the coverage of anti-glaucoma drugs till complete cessation of steroid therapy and intra ocular pressure stability.

In our study we found that immune-mediated corneal graft rejection is the leading cause of corneal graft failure in steroid group accounting for up to 85% of all failures in comparison with MMF group which accounts for 42% of all failures.

Thirteen cases had experienced rejection episodes in MMF group with tapering of the drug, 10 of them were reversible with increasing dose to full dosage. Three cases were irreversible despite full dosage of MMF. In steroid group 16 cases had rejection episodes in different periods, only 4 cases were reversible with full dose of systemic steroids and 12 cases had irreversible graft rejection.

Statistical analysis demonstrated a statistically significant difference between studied groups as regard state of corneal graft and showed that 72% of MMF group had clear corneal grafts, 16% had failed grafts and 12% had immune rejected grafts. The causes of failure were explained as retinal detachment in one case due to blunt trauma in the 7th month after having a completely clear graft and inflammation occurred due to suture removal that happened after one year of having a clear graft in three cases. Among cases having rejected grafts, one elderly case was non-compliant to treatment due to MMF side effects. She stopped MMF after only two months despite decreasing the dose. In steroid group, there were 48% rejection and 44% clear corneal graft and 8% failure.

Corneal graft rejection was defined by Guilbert et al, as an immune-mediated alteration of the graft by the host's immune system. Immune-mediated corneal graft rejection has been identified as the leading cause for corneal graft failure, accounting for up to 50% of all failures. Most immune rejection episodes occurred within the first 18 months following transplantation. Guilbert and co-workers reported an average keratoplasty to rejection time of 19.8 ± 20.4 months (range from 0.5 to 158 months) in a cohort of predominantly penetrating keratoplasties. Rejection episodes in this cohort led to graft failure in 53.8% of the cases[19].

Williams and co-workers reported registry data from selected high-risk keratoplasty cohorts (e.g., repeat keratoplasties, PK after infectious diseases such as herpetic keratitis/acanthamoeba infections, limbo-keratoplasty or PK in children) showed notably higher immune rejection rates, up to 90%[19].

Szaflik et al, also observed statistically significant differences in immune graft rejection and graft failure in his 2-

year-follow up study between the MMF group and control group receiving systemic steroid that during a mean of 24 months of observation, immune reactions occurred in eight cases (8%) and graft rejection with subsequent graft failure occurred in three cases (3%) in the MMF group. In the control group, graft rejection occurred in 76 cases (78%) and failure due to graft rejection occurred in 30 cases (31%). Kaplan-Meier analysis demonstrated that 93% of the grafts in the MMF-treated group and 47% in the control group showed no immune rejection ($p < 0.01$, log-rank test) after a year. Cox regression analysis proved that MMF treatment decreased the risk of graft rejection 11 times (RR = 11, 95.0 % CI 4.8-25, $p < 0.0001$)[20].

Study limitations found in our study are summarized in small sample size, short term follow up, high cost of drug and unavailability of corneal grafts.

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Data Availability: The authors declare that all data supporting the findings of this study are available within the article.

Competing interests: The authors declare no competing interests.

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Conflict of interest

All authors have no conflicts of interest that are directly relevant to the content of this review.

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