ARTICLE

Azithromycin in the treatment of gingival hyperplasia in renal allograft recipients on cyclosporine

AK Hooda, AS Narula
Department of Nephrology, Command Hospital, Central Command, Lucknow

Abstract

Background: Gingival hyperplasia is a known complication of Cyclosporine therapy. We studied the efficacy of azithromycin in the treatment of gum hyperplasia in renal transplant patients on follow-up in our center.

Methods: All renal transplant recipients with symptomatic gum hyperplasia were given Azithromycin for a period of 5 days in a dose of 500 mg on day 1 followed by 250 mg OD on days 2-5. The ratio of crown height and width in each of the 8 incisors was measured before starting therapy, at 4 weeks and at 8 weeks after therapy.

Results: There were 122 renal transplant recipients on our follow-up. Of these, 115 were on Cyclosporine. Out of these 11 patients (Males 9, Females 2) had symptomatic gum hyperplasia (9.56%). The symptoms in patients with gum hyperplasia were pain and bleeding from the gums. The average duration on Cyclosporine therapy in these patients was 25.8 months (3 to 36 months). Symptomatic relief was seen in all patients after Azithromycin therapy. The average value of ratio of crown height and width increased from pre-treatment baseline of 1.06 + 0.11 to 1.18 + 0.11 (at 4 weeks) and to 1.24 + 0.09 at 8 weeks after therapy ($p < 0.001$). The drug was well tolerated and none of the patients reported any side effects. There was no significant change in the creatinine level at 1 month after azithromycin therapy. Cyclosporine C2 assays done in 3 patients before and 4 weeks after therapy also showed no significant change.

Conclusion: We conclude that azithromycin is a safe and effective therapy for cyclosporine induced gum hyperplasia.

Key words: Gum hyperplasia, renal transplant, cyclosporine, azithromycin.

Introduction

Gingival hyperplasia is a known complication of Cyclosporine therapy and has been reported with a frequency between 21-25 % in renal transplant patients[1]. The pathogenesis underlying this complication has not yet been explained. Azithromycin, an antimicrobial agent derived from the macrolide antibiotic erythromycin, has been demonstrated to improve cyclosporine associated gingival hyperplasia. We studied the efficacy of azithromycin in the treatment of gum hyperplasia in the renal transplant patients on follow-up at our center.

Address for Correspondence:
Lt Col AK Hooda,
Classified Specialist
(Medicine & Nephrology)
Command Hospital,
Central Command,
Lucknow – 226002 (UP), India
E-mail : ashokhooda@hotmail.com

Material and methods

All renal transplant recipients with symptomatic gum hyperplasia were given azithromycin for a period of 5 days in a dose of 500 mg on day 1 followed by 250 mg OD on days 2-5. The ratio of crown height and width in each of the 8 incisors was measured before starting therapy, at 4 weeks and at 8 weeks after therapy. The measurements of the 8 teeth were averaged to give a single mean value per patient.

Results

There were 122 renal transplant recipients on our follow-up. Of these, 115 were on Cyclosporine. The average follow-up period was 45.7 months. In the study group

11 patients (Males 9, Females 2) had symptomatic gum hyperplasia (9.56%). None of the patients with gum hyperplasia were on Phenytoin or Nifedipine, though 7 of them were receiving Amlodipine, a calcium channel blocker. The symptoms in patients with gum hyperplasia were pain and bleeding from the gums. The dental hygiene in all these patients was satisfactory and none of them had required treatment for a dental illness in the previous 6 months. The average duration on Cyclosporine therapy in these patients was 25.8 months (3 to 36 months). Symptomatic relief was seen in all patients after azithromycin therapy. The average value of ratio of crown height and width increased from pre-treatment baseline of 1.06 ± 0.11 to 1.18 ± 0.11 at 4 weeks and 1.24 ± 0.09 at 8 weeks after therapy ($p < 0.001$). The drug was well tolerated and none of the patients reported any side effects. There was no significant change in the creatinine level at 1 month after azithromycin therapy. Cyclosporine C2 assays done in 3 patients before and 4 weeks after therapy also showed no significant change in C_2 level.

Discussion

Gingival hyperplasia is a known complication of cyclosporine therapy. It appears essentially as a papillary hyperplasia process affecting labial, buccal, palatal, and lingual tissues in all parts of the mouth. Although the pathogenesis underlying this complication has not yet been explained, there are at least two mechanisms that have been proposed. One is related to an interaction between the drug and gingival inflammation secondary to bacterial irritation. The other suggests that the drug might alter the complex cascade of biochemical events surrounding an inflammatory response, resulting in increased gingival connective tissue production[2]. Cyclosporine increases collagen synthesis by fibroblasts, decreases collagenase activity and increases levels of interleukin-6. Cyclosporine also has an indirect effect on collagen synthesis by reducing interferon-gamma, which is a strong inhibitor of collagen synthesis. Other than Cyclosporine, the factors that have been implicated in the development of gum hyperplasia are gingival inflammation, poor dental hygiene, use of phenytoin or calcium channel blockers, smoking and use of orthodontic and prosthetic applications.

Gingival hyperplasia has been reported with a frequency between 21 to 25% in renal transplant patients[1]. We found symptomatic gingival hyperplasia in 11 out of 115 (9.56%) patients on Cyclosporine. The average duration on CsA therapy in our patients was 25.8 months (3 to 36 months). The onset of gingival hyperplasia may be as early as within the first month of Cyclosporine treatment, however, there is a sharp increase in incidence around 3-6 months. Phenytoin and calcium channel blockers produce similar gum hyperplasia[3], and in one series the incidence of cyclosporine induced hyperplasia increased from 8% in patients on Cyclosporine alone to 51% in patients receiving Cyclosporine and Nifedipine[4]. None of our patients with gum hyperplasia were on phenytoin or nifedipine, though 7 of them were receiving amlodipine.

Changes of gum hyperplasia can be evaluated by measuring gingival sulcus depth, tooth length and length of inter-dental papillae. The changes usually involve the entire gingiva on both labial and buccal aspects, but may vary in severity over different regions. The incisors were chosen for assessment in our study based on the ease of accessibility for measurement. Gum hyperplasia can be very troubling in transplant recipients creating a potential source of infection in addition to being cosmetically unattractive. In addition to cosmetic reasons, the symptoms in patients with gum hyperplasia in our study were pain and/or bleeding from gums while eating food or on brushing the teeth. In some patients with severe, uncontrolled hyperplastic changes there is poor plaque control, significant alveolar bone loss and eventually tooth loss. These severe changes were not seen in our study group.

Treatment with azithromycin, an azalide antimicrobial agent derived from the macrolide antibiotic erythromycin, has been demonstrated to improve Cyclosporine associated gingival hyperplasia[5,6,7]. However, the mechanism by which azithromycin improves gingival hyperplasia is unknown. We gave azithromycin to our patients with gum hyperplasia for a period of 5 days in a dose of 500 mg on day 1, followed by 250 mg OD on days 2-5. Symptomatic relief was seen in all patients after azithromycin therapy. As an objective evidence of effectiveness of therapy, the ratio of crown height and width in each of 8 incisors was measured before starting therapy, at 4 weeks and at 8 weeks after therapy. The average value of ratio of crown height and width showed a significant increase from pre-treatment baseline of 1.06 ± 0.11 to 1.18 ± 0.11 at 4 weeks and 1.24 ± 0.09 at 8 weeks after therapy ($p < 0.001$). The drug was well tolerated and none of the patients reported any side effects. All our patients had stable graft function with a mean creatinine value of 1.2 mg/dl and there was no significant change in the creatinine level at 1 month after azithromycin therapy. Cyclosporine C2 assays done in 3 patients before and 4 weeks after therapy also showed no significant change.

Treatment with azithromycin is inexpensive and effective in a short period of time, avoiding gingival surgery in a large number of patients. For maximum efficacy, therapy should be initiated as early as possible, since the greater the degree of initial hyperplasia, the lower the benefits. In our study, only one patient had recurrence of gum hyperplasia after azithromycin therapy requiring gingivectomy. In some patients with severe gingival hyperplasia refractory to treatment, discontinuing

Cyclosporine and replacing it with tacrolimus (FK 506) may be appropriate as gingival hyperplasia is rarely observed in tacrolimus treated patients[8].

Conclusion

We conclude that azithromycin is a safe and effective therapy for CsA induced gum hyperplasia.

References

1. Pernu HE, Pernu LMH, Knuutila MLE, Huttunen KRH. Gingival overgrowth among renal transplant recipients and uraemic patients. Nephrol Dial Transplant 1993; 8: 1254-1258.
2. Brown RS, Beaver WT, Bottomley WK. The mechanism of drug-induced gingival hyperplasia. J Oral Pathol Med 1991; 20: 201-209.
3. Ramon Y, Behar S, Kishon Y, Engelberg IS. Gingival hyperplasia caused by Nifedipine – a preliminary report. Int J Cardiol 1984; 5: 195-204.
4. Thomason JM, Seymour RA, Rice N. The prevalence and severity of Cyclosporine and Nifedipine-induced gingival overgrowth. J. Periodontol 1995; 66: 572-578.
5. Gomez E, Sanchez-Nunez M, Sanchez JE, et al. Treatment of cyclosporine-induced gingival hyperplasia with azithromycin. Nephrol Dial Transplant 1997; 12: 2694-2697.
6. Kwun WH, Suh BY, Kwun KB. Effect of Azithromycin in the treatment of Cyclosporine induced gingival hyperplasia in renal transplant recipients. Transplantation Proc 2003; 35: 311-312.
7. Nash M, Zaltzman, J. Efficacy of azithromycin in the treatment of cyclosporine-induced gingival hyperplasia in renal transplant patients. Transplantation 1998; 65: 1611-1615.
8. Pirsch JD, Miller J, Deierhoi MH, Vincenti F, Filo RS. A comparison of Tacrolimus (FK 506) and Cyclosporine for immunosuppression after cadaveric renal transplantation. Transplantation 1997; 63: 977-983.