Mycophenolate mofetil: A novel immunosuppressant in Dystrophic Epidermolysis Bullosa

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Mycophenolate mofetil: a novel immunosuppressant in the treatment of dystrophic epidermolysis bullosa, a randomized controlled trial.

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Abstract

Background: No effective treatment has been found for epidermolysis bullosa dystrophica (EBD). Objective: To evaluate the efficacy and safety of mycophenolate mofetil (MMF) in treating EBD. Methods: This randomized controlled double-blinded study included 35 patients with severe generalized EBD. Patients were randomly divided into two groups: group I (18 patients) received cyclosporine therapy (5 mg/kg/day) and group II (17 patients) received MMF therapy (500-1500 mg/day). Clinical assessment was made weekly for 3 months from the start of the treatment. Patients were assessed by measuring the extent of the disease, the % of improvement, assessing the number of new blister formation and the time of complete healing of new blisters. Side effects were recorded when detected. Results: The % of improvement in the disease extent was statistically significantly higher (p = 0.009) in group I (mean ± SD: 59.21 ± 22.675) than in group II (mean ± SD: 44.03 ± 25.71). As regards the number of new blisters and the rate of healing of blisters, there was no statistically significant difference between both groups (p = 0.693 and 0.404, respectively). No serious side effects were reported. Conclusion: MMF seems to be a good therapeutic option for the long-term treatment of EBD, it can be a good alternative for patients who cannot tolerate cyclosporine.
EB dystrophica is one of the most devastating disorders known to man.

Many therapeutic options have been tried for this disorder including phenytoin, retinoids, antibiotics as tetracyclines, corticosteroids.

Unfortunately no effective treatment has been found to date.
The efficacy of cyclosporine in ttt of EBD was discovered accidentally after its use to prevent graft rejection in an EBD patient.

However, the long-term use of cyclosporine is always associated with undesirable side effects particularly interstitial renal fibrosis.
In our department, an EBD patient (6 years old), underwent a skin grafting operation for correction of syndactyly which occurred as a complication of the recurrent blistering affecting his fingers.

Cyclosporine (5mg/kg/day) was administered to prevent rejection but was not tolerated by the patient.
Cyclosporine was discontinued and replaced by Mycophenolate mofetil (MMF, 500 mg/day) as an alternative immunosuppressant.

Two weeks later, the daily spontaneous development of blisters was reduced by 70% (10 lesions/day to 2 lesions/day).
Introduction

- MMF is safely used for prolonged periods as an immunosuppressive agent for children, and has a wide safety margin.

- Thereby, we decided to try it for the first time in the treatment of EBD patients.
Methods

- This randomized, controlled, single blinded study was approved by the Dermatology REC, Faculty of Medicine, Cairo University.

- Written informed consents were obtained from the patients' parents/patient before starting treatment.
methods

- The study included **35 patients with EBD**.

- Diagnosis of EBD was based on a combination of:
  - Clinical,
  - Histopath exam.,
  - Immunofluorescence.
**Methods**

<table>
<thead>
<tr>
<th>Group I</th>
<th>Group II</th>
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<tbody>
<tr>
<td>18 patients; Cyclosporine (5mg /Kg/day)</td>
<td>17 patients; MMF (500-1500mg/day)</td>
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</table>

Final assessment was @ 12 weeks
### Methods

#### Clinical assessment:

<table>
<thead>
<tr>
<th>Extent of involvement</th>
<th>Rate of blister formation</th>
<th>Time of complete healing of new blisters</th>
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<tbody>
<tr>
<td><strong>Mild:</strong> less than 30% BSA, <strong>Moderate:</strong> 30-60% BSA, <strong>Severe:</strong> more than 60% BSA.</td>
<td><strong>Numerous:</strong> (more than 10 lesions/week), <strong>Few:</strong> (less than 10 lesions/week) or none.</td>
<td><strong>Delayed:</strong> (more than 6 days), <strong>Moderate:</strong> (3-6 days), <strong>Rapid:</strong> (less than 3 days).</td>
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</tbody>
</table>
Methods

- **Monitoring** of BP, CBC, liver enzymes, urea, creatinine was performed before treatment and every 2 weeks.

- **Side effects** were recorded when detected.
Before the ttt.
No statistical significant difference was found between both groups regarding:
- The extent of the disease,
- The number of new blisters/week
- The healing time of the developed blisters
Results

Group I
cyclsporine

Group II
MMF

After ttt (12 weeks)

both groups showed statistical significant improvement
(i) Disease extent,
(ii) Number of new blisters,
(iii) Rate of healing of blisters.
Results

Group I
- cyclsporine

Group II
- MMF

- % of improvement in the disease extent
- The number of new blisters appearance
- The rate of healing of blisters

significant improvement
Results
Side effects:

- No major side effects were reported.
- Only pruritus was reported equally in both groups.
- It was usually followed by new blisters.
- It was successfully controlled by cyproheptadine.
- New blister formation was also temporary accelerated in the summer time.
Results
Follow up

- We have followed the patients up to 18 months after the conclusion of the study and found that:

*Both drugs were well tolerated.*
Results

Group I
Results

Group I
Results

Group II
Results
Group II

a

b
The current study offers MMF as an effective therapeutic option for the long term treatment of EBD, with an acceptable safety margin.

It could be a good alternative for EBD patients who could not tolerate cyclosporine.
The mode of action of cyclosporine is not known.

It is assumed to be due to an immunosuppressive effect to an underlying immunological process that may play a role in the pathogenesis of EBD.
We hypothesize that MMF might increase expression of anchoring fibrils or type VII collagen or might have an anti-collagenase effect (under study).
Still, the mechanism of how immunosuppressive agents would be helpful in EBD is unclear.
Cyclosporine side effects:

- G.I.T. disturbances e.g. persistent vomiting
- Elevation of B P
- Renal fibrosis (long term administration)
- Immunosuppressive effects: early development of SCC.
Discussion

- MMF side effects:
  - Diarrhea
  - BM suppression *(doses as high as 3gm/day.)*

- The dose used in our study: *(500-1500mg/day)*, & is close to that recommended in organ transplanted children *(600-900mg/day).*
Incidence of malignancy e.g. SCC is so rare and has not been reported with the use of MMF alone.

In order to induce malignancy it has to be used with other immunosuppressive drugs a situation not encountered in ttt of EBD.
Conclusion

- MMF seems to be a good therapeutic option for the long term treatment of EBD.
- MMF can be a good alternative for patients who cannot tolerate cyclosporine.
- MMF dose should be increased during summer time as the incidence of blistering increases markedly during summer season, however the dose should never exceed 1500mg/day.
Large scale extended studies may shed more light on the long term validity & the assumed mechanism of action of this drug in the treatment of EBD.