TITLE: Mycophenolate Mofetil Tablets for Uveitis: A Review of the Comparative Clinical and Cost-Effectiveness

DATE: 25 May 2011

CONTEXT AND POLICY ISSUES

Uveitis is an inflammation within the eye from the uveal tract, which is made up of three structures – the iris, the ciliary body, and the choroid. Inflammation of these structures may result in symptoms such as eye pain, red eye, light sensitivity, tearing, blurred vision, seeing moving spots or flashing lights, or narrowing of the pupil, thereby affecting normal functioning of the eye. Uveitis may be idiopathic, or it may be associated with an underlying condition such as trauma, malignancy, infection, or an autoimmune disorder. If left untreated, uveitis can lead to permanent vision loss, and accounts for 10% of visual handicap in the Western world. It more frequently occurs in younger adults, and is the fifth most common cause of vision loss in persons aged 20 to 60 years.

Choice of treatment for uveitis is dependent on the underlying cause of the condition. Non-infectious uveitis is treated with topical and systemic corticosteroids, immunosuppressive drugs (e.g. methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, cyclophosphamide) that are intended to decrease symptoms and spare steroid use, and biologic therapies (e.g. infliximab, etanercept, adalimumab). Mycophenolate mofetil (MMF) is in the same class of immunosuppressive drugs as methotrexate and azathioprine, called antimetabolites. It has been reported to be effective in treating uveitis in many non-comparative studies (see Appendix), however its effectiveness and safety relative to other treatments for uveitis is not established. Recommended dosing of MMF in uveitis ranges from 500mg twice per day to 1500 mg twice per day. Based on the recommended dosing of MMF in uveitis and on its price in Canadian provincial drug formularies that reimburse this drug, the daily cost of MMF in uveitis ranges from $8.24 to $24.75, making it more expensive than other immunosuppressants listed in Canadian formularies.
The present review was undertaken to summarize the evidence for the comparative clinical effectiveness and cost-effectiveness of MMF in uveitis, with the aim of informing decisions regarding the use of this treatment.

RESEARCH QUESTIONS

1) What is the comparative clinical effectiveness of mycophenolate mofetil tablets for uveitis?
2) What is the cost-effectiveness of mycophenolate mofetil tablets for uveitis?

KEY MESSAGE

Evidence for the relative clinical benefit and safety of mycophenolate mofetil is limited and suggests some possible benefit versus azathioprine, and differing results versus methotrexate, however these results are inconclusive. No evidence for the cost-effectiveness of mycophenolate mofetil relative to other treatments in uveitis was identified.

METHODS

A limited literature search was conducted on key resources including PubMed, Ovid EMBASE, The Cochrane Library (2011, Issue 4), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2001 and April 25, 2011.

The resulting citations were then screened based on the selection criteria provided in Table 1.

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with uveitis (i.e. anterior uveitis, intermediate uveitis, retinal vasculitis, inflammatory chorionopathies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Mycophenolate mofetil tablets (also referred to as mycophenolic acid, mycophenolate, mofetil, cellcept, cell cept, myfenax, myfortic, cellmune, micocept, MMF, arzip)</td>
</tr>
<tr>
<td>Comparators</td>
<td>Steroids, azathioprine tacrolimus, cyclosporine, methotrexate, infliximab</td>
</tr>
</tbody>
</table>
| Outcomes            | Q1: reduction in inflammation of uveitis, decrease in symptoms, decrease in disease progression, toxicity, prevention of vision loss, clinical benefits, clinical harms. 
Q2: Economic evaluation outcomes |
| Study design        | Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations |

SUMMARY OF FINDINGS

The literature search yielded 245 citations, as well as 11 references from the grey literature. Abstracts were reviewed and three studies that described comparative evaluations of MMF were selected for further screening. All three studies\(^\text{10-12}\) fulfilled the selection criteria and were included in this report. All three studies were non-randomized clinical assessments. No health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, or economic evaluations were identified.
Clinical Effectiveness of MMF

Galor et al.¹⁰ (2008) conducted a retrospective study to assess the relative effectiveness and side effect profiles of antimetabolite immunosuppressive drugs (methotrexate, azathioprine, MMF) in 257 patients with non-infectious ocular inflammation. The authors retrospectively analyzed data obtained from patient files at an eye institute in the United States. Patients who were treated with an antimetabolite drug as first line therapy were included in the study. Patients who had less than three months follow-up, had previous prednisone therapy, or had active ocular inflammation with ≤10 mg/d prednisone were excluded from the study. Main outcome measures were control of inflammation, which for uveitis was defined according to the Standardization of Uveitis Nomenclature Working Group Criteria (rare cells or less as detected by high-power field in the anterior chamber (grade 0, grade range 0 to 4) or vitreous and no new retinal or choroidal lesions), treatment success, defined as the ability to control ocular inflammation, and corticosteroid–sparing success, defined as a tapering of the prednisone dose to ≤10 mg/day. Side effects were assessed by patient history and laboratory evaluations.

Three-hundred and twenty-one patients (128 treated with methotrexate, 45 with azathioprine, and 148 with MMF) were screened according to study criteria and 257 of these patients were included in the study (90 methotrexate, 38 azathioprine, 129 MMF). The average age of patients in the three groups was 42 years (range: 6-87 years)(methotrexate), 53 years (range:20-82 years)(azathioprine), and 49 years (range:13-80 years)(MMF), (p<0.001). There were between-group differences with regard to previous treatment with an immunosuppressive drug (methotrexate: 9%, azathioprine: 34%, MMF:17%; p=0.001). There were no between-group differences in gender distribution or diagnosis; sixty-five percent were female, and approximately 67% of patients had a diagnosis of uveitis, 20% had a diagnosis of scleritis, and the remaining 13% had other ocular conditions. Median disease durations in the three groups were 19 months (methotrexate), 33 months (azathioprine) and 18 months (MMF), however these differences were not statistically significant (p=0.42). The median starting doses of the three antimetabolites were 15mg/week for methotrexate, 150 mg/day for azathioprine, and 2000 mg/day for MMF. The median starting dose of prednisone was significantly higher in azathioprine (35mg/day) and MMF (45mg/day) compared with methotrexate (15mg/day), (p<0.001). In contrast, the proportion of patients in whom the dose of antimetabolite therapy was increased was higher in the methotrexate group (64%) compared with azathioprine (32%) and MMF (36%), (p<0.001). The authors conducted further analyses to explain this two-fold difference with methotrexate, and found that 70% of treatment successes with methotrexate occurred with prednisone dosages between 15 and 20 mg/week, suggesting that dosages lower than 15 mg/week were less effective in this combination. A second immunosuppressive agent was added in 20% of patients taking methotrexate, 15% of patients taking MMF, and 0% of patients taking azathioprine (p=0.01). Kaplan-Meier incidence curves were used to estimate time to corticosteroid-sparing success. This analysis showed significant differences in incidence rates of treatment success (number of events divided by the number of person-years at risk) between the MMF and methotrexate groups (1.68 versus 0.90, respectively; p=0.002) but not between MMF and azathioprine (1.68 versus 0.96, respectively; p=0.37). Multivariate Cox regression analysis was used to compare time to treatment success in the three groups, while controlling for age, previous use of immunosuppressives, starting prednisone dose, and disease duration. The results of this and other outcomes defining treatment success are given in Table 2.
Table 2: Treatment outcomes of three antimetabolite immunosuppressive drugs in noninfectious ocular inflammation, Galor et al.\textsuperscript{10} (2008)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Methotrexate</th>
<th>Azathioprine</th>
<th>MMF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to treatment success* (months)</td>
<td>6.5</td>
<td>4.8</td>
<td>4.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Corticosteroid-sparing success after 6 months (% patients)</td>
<td>42%</td>
<td>58%</td>
<td>79%</td>
<td>NR</td>
</tr>
<tr>
<td>Median time to discontinuation of prednisone (months)</td>
<td>38</td>
<td>46</td>
<td>31</td>
<td>NR</td>
</tr>
<tr>
<td>Discontinuation of prednisone after 6 months (% patients)</td>
<td>6%</td>
<td>6%</td>
<td>12%</td>
<td>0.47</td>
</tr>
<tr>
<td>Rate of treatment discontinuation due to lack of efficacy (patients/person-year)</td>
<td>0.16</td>
<td>0.07</td>
<td>0.09</td>
<td>0.06</td>
</tr>
</tbody>
</table>

\*MMF=mycophenolate mofetil; NR=not reported; \*defined as requirement for ≤10 mg/day of prednisone.

With regard to side-effects, this rate was higher in the azathioprine group (0.29/person-year) compared with the methotrexate (0.14/person-year), and MMF (0.18/person-year). More patients on azathioprine experienced hematologic abnormalities. The authors noted that study limitations included the tendency to dose methotrexate lower at the start, compared with azathioprine and MMF. They did not expect ascertainment bias to affect their results as patients in their clinic were seen regularly on a monthly basis. They noted that their center tends to see more serious cases of ocular inflammation, which may have had an impact on corticosteroid-sparing success, but they did not expect this to impact treatment groups differentially. The authors concluded that their data suggest that time to control of ocular inflammation was faster with MMF than with methotrexate, and that azathioprine has higher treatment-related side-effects than either methotrexate or MMF.

Schatz et al.\textsuperscript{11} (2007) reported on the effectiveness and complications of different immunosuppressants used in a steroid-sparing strategy for children with uveitis in France. It is unclear from the description of the methods if the study was performed prospectively, or if this was a retrospectively conducted analysis. Forty children with non-infectious uveitis were followed for a period of five years. All patients underwent ophthalmologic and clinical assessments. The average age of the patients was 6.5 years (range: 3 months to 14 years), and 23 were male. All patients received topical corticosteroid drops and mydriatics. Thirty (75%) patients received systemic corticosteroid therapy. An immunosuppressant was used in combination with steroids in cases where high-dose systemic steroids (>30mg/m\textsuperscript{2}) were required for more than three months. The choice of immunosuppressant was based on the patient’s underlying disease. Methotrexate was used for rheumatoid conditions. Etanercept was used in juvenile rheumatoid arthritis or spondyloarthropathy, or in cases of partial resistance or dependency to corticosteroids. Cyclosporine was used where patients were resistant to steroids in combination with azathioprine. MMF was specifically used in cases where azathioprine was inefficacious, and azathioprine was the gold standard when no underlying disease existed. Sixteen patients received MMF under these criteria. Other immunosuppressants prescribed included methotrexate, cyclosporine, and etanercept. The authors reported a 61% (range: 48% to 77%) improvement in visual acuity in patients taking a combination of azathioprine and systemic steroids, and a 94% (range: 50% to 97%) improvement in visual acuity among patients taking MMF. Changes in visual acuity were not reported for the other immunosuppressants.
Twenty-three of the 40 patients experienced ocular complications, and five experienced systemic complications, however these complications were not reported by treatment. No complications associated with high-dose steroid use were noted. The authors concluded that the combination of systemic corticosteroids and immunosuppressants allows for good recovery in visual acuity with few complications and side effects.

Baker et al.\textsuperscript{12} (2006) compared the retention time of immunosuppressive agents prescribed to 107 patients with inflammatory eye disease, 69 (64\%) of whom had uveitis, 24 (22\%) of whom had scleritis-type conditions, and 14 (13\%) of whom had other inflammatory eye conditions. Treatment retention time (the period of time a patient continues to take a drug) was considered to be an indicator of effectiveness and tolerability. Clinical records from patient visits taking place at an eye clinic in the United States over a one year period were reviewed, and data on patient characteristics and treatment were extracted. A cox regression analysis, adjusted for clustering to account for patients receiving more than one drug, was performed to compare other drugs against methotrexate. The average age (and standard deviation) of patients included in the analysis was 49.0±17.6 years, and 32 (30\%) were male. One-hundred and ninety-three uses of immunosuppressive drugs were determined. The five most commonly used drugs were methotrexate (66 uses), cyclosporine (37 uses), azathioprine (26 uses), mycophenolate mofetil (22 uses), and cyclophosphamide (15 uses), with 27 uses determined to have occurred in seven other drug treatments. The median retention time for the five most commonly used immunosuppressants was 1,216 days with methotrexate, 426 days for cyclosporine, 303 days for azathioprine, 274 days for mycophenolate mofetil, and 487 days for cyclophosphamide. Median retention time was not reported for the seven other drug treatments. While reasons for cessation of treatment were reported, they were not given by drug therapy. The authors reported the results of their regression analysis for all patients combined, as well as for 63 of the 69 patients with uveitis, and these results are shown in Table 3.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>All patients (166 observations in 101 patients)</th>
<th>Uveitis only (104 observations in 63 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>p value</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>2.19</td>
<td>0.004</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>2.00</td>
<td>0.04</td>
</tr>
<tr>
<td>MMF</td>
<td>2.29</td>
<td>0.04</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>4.31</td>
<td>0.001</td>
</tr>
</tbody>
</table>

CI = confidence interval

The authors did not report the reasons why some patients had been excluded from the regression analyses. To account for the potential bias of including patients who discontinued therapy because of disease remission, the authors conducted an additional analysis (for all cases of ocular inflammation) where they excluded 15 such patients, and reported similar results to those seen in the analysis of all 107 patients. It is noted that the authors did not measure or control for concomitant corticosteroid use in their analyses. The authors concluded that methotrexate may offer a superior combination of effectiveness and tolerability over other commonly used corticosteroid-sparing immunosuppressive agents.
Limitations

Very few comparative studies of MMF versus other treatments in uveitis were identified, none of which were randomized studies.

Patients in all three reviewed studies\textsuperscript{10-12} had exposure to more than one immunosuppressant therapy, however two\textsuperscript{10,12} of these studies attempted to control for this exposure through multivariate analysis.

Prior exposure to other treatments in each of the three studies does not permit an assessment of MMF and its comparators as first-line therapy.

Sample sizes in two studies were relatively small (N=40 in Schatz et al., and N=69 in Baker et al.)\textsuperscript{11,12} This may have impacted statistical significance in a sub-analysis of uveitis patients in one study\textsuperscript{12}

Incomplete and inconsistent reporting of results was noted in one study.\textsuperscript{11}

Two studies\textsuperscript{10,12} included patients with inflammatory eye conditions other than uveitis, however one of these studies\textsuperscript{12} conducted sub-analyses with uveitis patients only.

It is not clear if dosing was comparable between treatments (i.e. maximum effective dose) in each of the three studies. One study\textsuperscript{10} indeed noted that there were differences.

One study\textsuperscript{12} used a proxy outcome (treatment retention time) for efficacy and tolerability combined. In addition, this study did not assess or control for concomitant corticosteroid use in its multivariable analyses, which could have impacted its observed findings.

Study data were obtained from a single clinical practice in two of the studies.\textsuperscript{10,12}

No economic evaluations were identified.

**CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING**

A review of the literature on MMF in uveitis resulted in the retrieval of three reports, all of which were relevant to clinical effectiveness, and none of which addressed the cost-effectiveness of MMF. Each of the three studies had some degree of bias in its methods.

One retrospective analysis\textsuperscript{10} evaluated therapy with methotrexate, azathioprine, and MMF, and this analysis suggested better control of ocular inflammation with MMF than with methotrexate, and a similar side-effect rate with methotrexate (both of which were lower than the side-effect rate observed with azathioprine). While this study made efforts to control for several potential biases in their analyses, it is possible that patients given methotrexate were not given an effective initial dose as patients who were given azathioprine or MMF. It is of note that only 67% of the patients in this study had uveitis.
A second study\(^1\) suggested better improvements in visual acuity in patients taking MMF compared with azathioprine, however patients taking MMF had previously been exposed to azathioprine. This analysis was found to be generally poorly controlled and reported.

The study by Baker et al.\(^12\) reported longer treatment retention times with methotrexate compared with MMF in patients with ocular inflammation, as well as in a subset of patients with uveitis, however this latter finding was not statistically significant. Retention time is a proxy for clinical benefit, which was not directly assessed in this study. At the same time, this study did not control for concurrent corticosteroid use in its multivariate analyses, which could have impacted retention times.

While it is possible that there may be some benefit of MMF relative to other treatments in uveitis, the data retrieved for this review make it difficult to draw conclusions, and there is insufficient evidence to consider relative the effectiveness of the comparators as first-line therapy. Randomized trials and economic evaluations of MMF and its comparators are needed to better evaluate its clinical and cost-effectiveness in uveitis.

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REFERENCES


APPENDIX: Additional information

Non-comparative studies of mycophenolate mofetil in uveitis


