Clinical Outcomes of Patients with Ocular Mucous Membrane Pemphigoid (OcMMP) Based on their Direct Immunofluorescence (DIF) Biopsy Results

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Introduction

- Mucous membrane pemphigoid (MMP) is a progressive autoantibody-mediated disease that leads to conjunctival scarring and corneal blindness.
- According to the recommendations of the First International Consensus on mucous membrane pemphigoid (2002), a positive direct immunofluorescence (DIF) biopsy is needed before the diagnosis of MMP can be confirmed[1]
- However, the disease exists in a cohort of patients who are DIF biopsy negative.
- The disease progression in this subset of patients may differ and potentially be more severe compared to biopsy positive patients[2]

Aim and objectives

Aim: The aim of this study is to determine whether DIF status has an impact on the clinical outcomes of patients with MMP.

Objectives:
- To characterise the clinical demographics and outcomes of a large MMP cohort at the Birmingham and Midland Eye Centre (BMEC).
- To perform a systematic review and meta-analysis on existing literature and our cohort findings to determine overall outcomes of MMP patients stratified by DIF biopsy status.

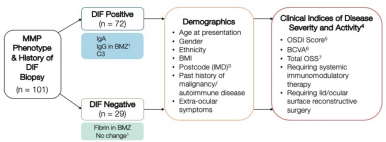
Method

Our cohort at Birmingham and Midland Eye Centre:
Involved identifying patients retrospectively via biopsy logs (1998 – 2019) at the BMEC.
101 patients fulfilled our **Inclusion Criteria** by having:
- The clinical phenotype of MMP **and**
- Undertaken direct immunofluorescence biopsies (DIF) on perilesional conjunctival tissue and/or oral mucosa.

Exclusion Criteria who made patients ineligible included*:*
- No history of undertaking DIF biopsy.
- Progressive cicatrising conjunctivitis due to other causes.

Figure 1 below illustrates the study design for our cohort, which includes the classification of participants in addition to the type of data collected.

Figure 1. Study Design for Our Cohort



Abbreviations: *BMZ, Basement membrane zone; BMI, Body Mass Index; IMD, Index of Multiple Deprivation; OSDI, Ocular Surface Disease Index; BCVA, Best corrected visual acuity; OSS, Ocular Staining Score.*

The main three indices used for our cohort to quantify the disease progression:
- Ocular Surface Disease Index (OSDI) score
- Best Corrected Visual Acuity (using the LogMAR Scoring)
- Total Ocular Staining Score (OSS).

The two main markers used for our cohort to quantify disease severity:
- **Disease activity index:** requirement of systemic immunomodulatory therapy including the use of systemic corticosteroids, dapsone, sulfasalazine, methotrexate, azathioprine, mycophenolate, or cyclophosphamide, ciclosporin, or tacrolimus.
- **Disease damage index**: requirement of reconstructive surgery for cicatricial lid deformities and ocular surface failure such as amniotic membrane graft, conjunctival graft transplant, limbal stem cell transplant, forniceal reconstruction, entropion repair, conjunctivoplasty, or lamellar resection.

Systematic review and meta-analysis:
- The databases searched to extract our studies are Embase, CAB Abstracts, Ovid MEDLINE and In-Process & Other Non-Indexed Citations. The main terms revolve around the variants of the terms "direct immunofluorescence biopsy" and "mucous membrane pemphigoid".

Figure 2. Study Selection Criteria for Inclusion in Systematic Review and Meta-analysis

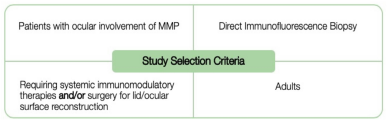
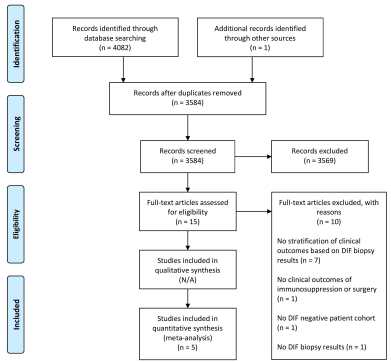


Figure 3. PRISMA Diagram of Studies Included in the Quantitative Svnthesis



Results

Birmingham and Midland Eye Centre (BMEC) study population
- No major differences in most demographics collected between DIF positive and DIF negative groups were found. The following exceptions were noted:
  - Patients in the DIF negative group are significantly more likely to be likely to be female (p-value= 0.042) and of older age (p-value= 0.022).
  - DIF positive patients are more likely to have extra-ocular symptoms of MMP compared to DIF negative patients (p-value= 0.030).
- Subgroup analysis of systemic immunomodulatory therapy showed no significant differences in usage for all immunomodulatory drugs between the two groups, as illustrated in **Table 1**, with exception to use of cyclophosphamide.
- Cyclophosphamide was significantly more likely to be used by DIF negative patients (p= 0.033).
- DIF negative patients were also found to be significantly more likely to be using tetracycline and topical immunosuppression (p= 0.016).

Table 1. Clinical Indices of Disease Severity, Activity and Damage

	All MMP	n	DIF positive	n	DIF negative	n	p-value
OSDI score	**29.5** (10.4 – 56.0)	82	**27.0** (7.5 – 52.0)	59	**45.5** (20.0 – 80.0)	23	**0.007**
BCVA	**0.28** (0.10 – 0.52)	100	**0.2** (0.00 – 0.50)	71	**0.30** (0.20 – 1.10)	29	0.136
Total OSS	**4** (1 – 6)	82	**3** (1 - 6)	59	**4** (3 – 9)	23	**0.010**
Disease Activity Index:							
Requiring systemic immunomodulatory therapy	**82** (81%)	101	**61** (84.7%)	72	**22** (76%)	29	0.389
Disease Damage Index:							
Requiring lid/ocular surface reconstructive surgery	**38** (38%)	101	**26** (36.1%)	72	**13** (45%)	29	0.499

- In our cohort, DIF negative patients had significantly worse outcomes in OSDI score and Total OSS.
- There were no significant differences between both groups with regards to both markers of disease severity used:
  - **Disease activity index.**
  - **Disease damage index**.

Meta-analysis of published literature results
- One study, by Francis et al., was not included in either of the meta-analyses since the study only consisted of four patients, meaning that the data was not estimable for meta-analyses.

Figure 4. Forest Plot Comparing the Odds of Treatment with Systemic Immunomodulatory Therapies and Direct Immunofluorescence Biopsy Status

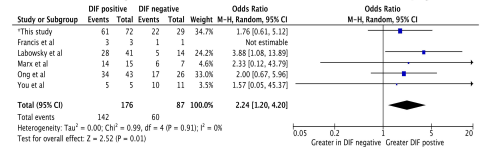
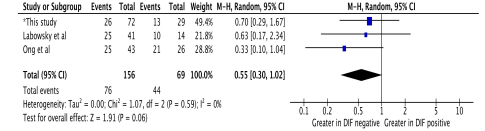


Figure 5. Forest Plot Comparing the Odds of Requiring Lid and/or Ocular Surface Reconstructive Surgery and Direct Immunofluorescence Biopsy Status



Conclusions

- In our cohort, there were no major clinical demographic differences between DIF positive and DIF negative patients.
- DIF negative patients reported significantly worse clinical indices of disease severity and activity in our cohort.
- Our study supports the current existing published literature.
- In the meta-analysis, DIF positive patients were significantly more likely to be treated with immunomodulatory therapies. This could potentially be attributed to the uncertain diagnosis in DIF negative when based on the 2002 international consensus.
- Trends in the meta-analysis show that there is a higher proportion of DIF negative patients needing lid/ocular surface reconstructive surgery.

We therefore propose the following two key recommendations:
- Current diagnostic criteria of MMP should be broadened to better account for DIF negative patients.
- It is important to start immunomodulatory and anti-fibrotic treatment in DIF negative patients.

Disclosure

None of the authors(K. Suleiman[1,2]; L. Low[1,2]; M.R. Davidson[1,2]; K. Tsang[1,2]; G.R. Wallace[1,2]; S. Rauz[1,2]) have any commercial relationships or any conflicts of interest regarding the materials discussed in this presentation.

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