Corticosteroid-induced remission and mycophenolate maintenance therapy in granulomatous lymphocytic interstitial lung disease: long-term, longitudinal change in lung function in a single-centre cohort

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The use of MMF is associated with long-term effectiveness in GLILD and permits weaning of corticosteroids. A delay in initiating and continuing maintenance treatment could lead to disease progression. https://bit.ly/3PXShAd

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Abstract

Aim The aim of the study was to evaluate the response in lung function to different treatment regimens for common variable immunodeficiency patients with granulomatous lymphocytic interstitial lung disease (GLILD).

Method A longitudinal retrospective cohort study was carried out. Patients were divided into three groups. To assess the response to different treatments, we compared baseline lung function with post-treatment tests.

Results 14 patients with GLILD were included, seven of whom were treated with acute corticosteroids for a mean duration of 132±65 days. Spirometry results were unchanged, but there was a significant improvement in diffusing capacity of the lung for carbon monoxide (D_{LCO})% and transfer coefficient of the lung for carbon monoxide (K_{CO})% (median change in D_{LCO}%=7%, p=0.04, and K_{CO}%=13%, p=0.02). Relapse occurred in three out of seven patients. Five patients were treated with long-term mycophenolate mofetil (MMF) with/without corticosteroids for a mean duration of 1277±917 days. No changes were found in spirometry; however, there was a significant increase in D_{LCO}% and K_{CO}% (median change in each of D_{LCO}% and K_{CO}%=10%, p=0.04). Four patients on steroids with MMF successfully weaned the prednisone dose over 12 months. Four patients never received immunosuppression therapy. A significant decline was found in their lung function assessed over 7.5 years. The median reduction in the forced vital capacity (FVC)%, forced expiratory volume in 1 s (FEV_1)% and D_{LCO}% was 15%, 7% and 15%, equivalent to 2%, 1% and 2% per year, respectively.

Conclusion Corticosteroids improve gas transfer in GLILD, but patients often relapse. The use of MMF was associated with long-term effectiveness in GLILD and permits weaning of corticosteroids. A delay in initiating and continuing maintenance treatment could lead to disease progression.

Introduction

Common variable immunodeficiency disorders (CVID) are the most common symptomatic primary immune deficiencies with a prevalence of between 1 in 25 000 and 1 in 50 000 [1]. CVID is characterised

by hypogammaglobulinaemia and increased risk of infection, which can be mitigated with immunoglobulin replacement therapy (IgRT). IgRT aims to decrease the number of infections but does not appear to play a significant role in preventing or reducing non-infectious complications. Non-infectious complications such as autoimmunity, splenomegaly, gastrointestinal disease, lymphocytic infiltration and/or granulomatous inflammation affect up to 33% of CVID patients [2].

Chronic lung disease is very common in CVID. Bronchiectasis resulting from acute infections is the commonest manifestation. 20 to 30% of CVID patients develop multi-system immune dysregulation associated with increased mortality [3], which in some people affects the lung and is called granulomatous and lymphocytic interstitial lung disease (GLILD). GLILD has been defined by the British Lung Foundation/United Kingdom Primary Immunodeficiency Network (BLF/UKPIN) Consensus Statement as "a distinct clinico-radio-pathological interstitial lung disease occurring in patients with CVID, associated with a lymphocytic infiltrate and/or granuloma in the lung, and in whom other conditions have been considered and where possible excluded" [4]. Pulmonary function tests (PFTs) and computed tomography are essential tools to identify the disease, which can only be confirmed definitively using biopsy.

There is little scientific evidence regarding effective treatment of GLILD, and management is mainly based on experts' views. A 2021 systematic review reporting treatment strategies for GLILD illustrated the controversy over the effectiveness of treatments [5]. Clinicians in the BLF/UKPIN Consensus Statement agreed that, when treatment is necessary, glucocorticoids should be the first-line therapy for GLILD after optimising IgRT. Rituximab, azathioprine and mycophenolate were agreed to be second-line treatments, either alone or in conjunction with corticosteroids. Mycophenolate mofetil (MMF) is an immunomodulatory agent which inhibits lymphocyte proliferation. However, there is lack of evidence supporting its efficacy in GLILD. Our objective was to report the first long-term, longitudinal cohort study of all patients with GLILD from a single large centre and to use this to evaluate the response of lung function to different treatment regimens, specifically 1) acute corticosteroids to induce remission and 2) MMF to maintain remission, in comparison to IgRT only.

Methods

This is a longitudinal retrospective cohort study from a single centre, the Royal Free Hospital, London, UK. This is the largest UK centre for GLILD. We retrospectively reviewed the demographic and physiological data of all patients with CVID and GLILD who were treated and followed between 2010 and 2021. The electronic medical records of 23 patients were reviewed. The diagnosis of CVID was based on current international guidelines [6], while the diagnosis of GLILD was based on a local protocol, consistent with the BLF/UKPIN diagnosis described above [4]. Bronchoscopy with bronchoalveolar lavage was generally performed to exclude infection, and video-assisted thoracoscopic surgery lung biopsy was often (but not always) performed to eliminate other diagnoses and confirm granulomatous and or lymphocytic lung infiltration. Immunoglobin serum levels prior to each period under study, and the median levels during each period of study (taken at the time of IgG trough), were calculated. Values reported as $<0.1\ g{\cdot}L^{-1}$ were replaced with $0.05\ g{\cdot}L^{-1}$ to permit analysis. All patients were receiving IgRT. Lymphocyte subsets prior to and during the period of study were also evaluated.

We included all living and deceased GLILD patients who were followed at our hospital during this period. We divided patients into the following groups based on the treatment regimen received, defined further below: 1) patients who received an acute dose of corticosteroid to treat GLILD in an attempt to achieve disease remission; 2) patients who received long-term MMF with or without corticosteroids to maintain disease remission; and 3) patients who received no treatment other than IgRT. Patients could be included in multiple groups if there was at least a 6-month gap between the treatments. Regardless of how many courses of a single treatment the patient received, only the first course was included. Comparison of lung function parameters (see below), before and after treatment, was used to assess treatment response.

The inclusion criteria for the acute steroid group comprised receiving a new daily dose of corticosteroids equal to or >30 mg oral prednisolone, no previous chronic daily dose of corticosteroids exceeding 7.5 mg prednisolone, and, if using previous corticosteroids, an absolute minimal increase of 30 mg, and no other immunosuppression. To assess the response to treatment, baseline lung function was required to be within 6 months before starting treatment; the post-treatment PFT was taken as the first one after the corticosteroid dose had been decreased again to <30 mg. For the chronic MMF group, we included patients who received MMF alone or with corticosteroids and had been on MMF for at least 4 months. Three patients had MMF initiated with acute steroids; the MMF continued as the steroid was weaned. The baseline lung function was the first test before initiating MMF, and two follow-up PFTs were required to assess the long-term response to the treatment. The third group received immunoglobulin replacement only. All GLILD patients

who were monitored and did not receive any immunosuppressive treatment for GLILD were included in this analysis. To assess lung function change over time, we calculated the absolute and relative change between the first and last PFT results available.

Pulmonary function testing

American Thoracic Society/European Respiratory Society Task Force Guidelines were used as a reference for performing and interpreting all PFT, which were performed in our hospital laboratory by trained technicians. Parameters such as forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and lung carbon monoxide diffusion capacity (D_{LCO}) were collected. Owing to the inconsistency of the reference equations that were used to normalise the lung function tests over time, all lung function results were recalculated using the Global Lung Function Initiative calculators for spirometry, D_{LCO} and lung volume (http://gli-calculator.ersnet.org/).

Statistical analysis

Numbers and percentages were used to report categorical data. Mean±SD or median and interquartile range (IQR) were used to report continuous data. The median change was reported in % points. Nonparametric Wilcoxon signed-rank tests were used to analyse pre-treatment and post-treatment continuous variables because the dataset was small. Data analyses used SPSS (version 23). $p<0.05$ was assumed to be statistically significant. The study had ethics approval as part of an umbrella application, and all participants provided written informed consent (REC 04/Q0501/119).

Results

Study population

For this study, we identified 23 patients with GLILD from our records at the Royal Free Hospital from January 2010 to September 2021. Nine patients were not included in the analyses because they had no baseline PFT (n=3), they were on long-term low-dose corticosteroids (n=3) or they received other immunosuppressive regimes (including rituximab and azathioprine) during treatment (n=3).

The GLILD cohort included in this report consisted of 14 patients. Characteristics are reported in table 1. Of these patients, 43% were male with a mean age of 52±14 years. The majority of patients had splenomegaly (93%). Nine patients (64%) developed other autoimmune complications.

10 patients (71%) had coexistent radiological bronchiectasis. Histological findings of organising pneumonia, lymphocytic interstitial pneumonia or granuloma were found in seven out of seven patients who had a lung biopsy. Six patients (43%) had extrapulmonary granulomatous disease affecting the liver, lymph nodes or uvea. Genetic investigations were available in 12 patients (86%), only three of whom had an identified gene diagnosis: SOCS1 haploinsufficiency, CTLA-4 haploinsufficiency and PTPN2 deficiency. All patients were receiving IgRT (400–800 $mg \cdot kg^{-1} \cdot month^{-1}$).

TABLE 1 Patient characteristics (n=14)

Sex	
Male	6 (43)
Female	8 (57)
Age years	52±14
Age at CVID diagnosis years	32±16
Smoking	
Non-smoker	12 (86)
Former smoker	2 (14)
Autoimmune manifestations	
Splenomegaly	13 (93)
ITP	6 (43)
AIHA	4 (29)
Uveitis	3 (21)
Neutropenia	2 (14)
Other; plaque psoriasis, rheumatoid arthritis	2 (14)

Data are presented as n (%) and mean±SD. CVID: common variable immunodeficiency disorder; ITP: immune thrombocytopenic purpura; AIHA: autoimmune haemolytic anaemia.

Immunological parameters

The median serum immunoglobulin levels for patients prior to starting acute steroids are reported in table 2, demonstrating adequate immunoglobulin replacement. IgA deficiency was present in 93% of patients. Lymphocyte subsets are also reported in table 2, and a deficiency in $CD3^+$, $CD4^+$, $CD8^+$ and $CD19^+$ cells counts was found in 21%, 14%, 36% and 50% of patients, respectively. 13 patients (93%) had significantly decreased numbers of natural killer (NK) cells. The EUROClass of the different treatment groups is also reported in table 2. 13 patients (93%) had % B-cells >1% of total lymphocytes. Of these, eight patients (57%) had switched memory B-cells >2% and six of them had $CD21^{low}$ B-cells ⩾10%. Five patients (36%) had switched memory B-cells ⩽2%, <9% transitional B-cells and $CD21^{low}$ B-cells ⩾10%. Only one patient had very low B-cell numbers (<1%).

As also reported in table 2, there were no significant changes in levels of IgG (p=1.00, p=0.14), IgA (p=0.85, p=1.00) and IgM (p=0.06, p=0.14) following the introduction of acute steroids or MMF and/or steroids. Following introduction of acute steroids, there was a significant decrease in the numbers of $CD3^+$ (p=0.03), $CD4^+$ (p=0.03) and NK cells (p=0.04). There were no significant changes found in lymphocyte subsets in patients commencing MMF or in the IgRT-only group.

Baseline lung function interpretation

Of the 14 GLILD patients, nine (64%) had normal baseline spirometry. Four (28%) had a restrictive pattern defined by reduced FEV_1 and normal or increased FEV_1/FVC ratio. One (7%) patient had obstructive lung function defined by normal FVC, low FEV_1 and low FEV_1/FVC ratio. D_{LCO} measurements were abnormal in 12 (86%).

Lung function response to acute corticosteroids

Seven patients received a new prednisone dose of ⩾30 mg. The median time between diagnosis of GLILD and acute steroid initiation was 1 year (IQR 0–11). The mean daily dose at initiation was 49±12 mg·day^{-1} (0.5–1 mg·kg^{-1}·day^{-1}). The mean duration of acute corticosteroid use was 132±65 days, and the mean

TABLE 2 Laboratory characteristics of granulomatous lymphocytic interstitial lung disease patients

Laboratory characteristic	Acute steroid	Chronic MMF±corticosteroids	Immunoglobulin replacement
Serum immunoglobulin levels prior to period under study g·L^{-1}			
IgG	9.70 (8.30–10.40)	8.00 (6.70–11.15)	10.15 (6.60–14.38)
IgA	0.05 (0.05–0.10)	0.05 (0.05–0.50)	0.05 (0.01–0.16)
IgM	0.70 (0.50–1.30)	0.70 (0.08–2.70)	0.15 (0.06–0.28)
Trough immunoglobulin levels during period under study g·L^{-1}			
IgG	9.50 (8.93–11.60)	10.70 (10.20–11.90)	10.55 (10.05–12.70)
IgA	0.05 (0.04–0.16)	0.05 (0.05–0.50)	0.05 (0.05–0.31)
IgM	0.30 (0.16–0.90)	0.30 (0.05–1.30)	0.05 (0.05–0.24)
Lymphocyte subsets count prior to period under study ×10^9 per L			
Lymphocyte count	1.09 (0.85–1.21)	1.32 (0.68–1.70)	1.07 (0.72–2.03)
CD3	0.96 (0.82–1.01)	1.01 (0.55–1.28)	0.81 (0.55–1.33)
CD4	0.59 (0.35–0.73)	0.44 (0.28–0.77)	0.61 (0.42–0.71)
CD8	0.25 (0.20–0.42)	0.35 (0.22–0.63)	0.14 (0.09–0.76)
CD19	0.04 (0.02–0.09)	0.20 (0.10–0.23)	0.15 (0.10–0.39)
CD16+CD56	0.08 (0.03–0.38)	0.08 (0.02–0.13)	0.08 (0.05–0.12)
Lymphocyte subsets count during period under study ×10^9 per L			
Lymphocyte count	0.78 (0.43–1.17)	1.13 (0.55–1.87)	0.60 (0.28–1.13)
CD3	0.66 (0.39–0.98)	0.88 (0.48–1.29)	0.40 (0.19–0.93)
CD4	0.32 (0.22–0.65)	0.43 (0.27–0.74)	0.35 (0.18–0.38)
CD8	0.24 (0.18–0.29)	0.29 (0.17–0.59)	0.06 (0.03–0.51)
CD19	0.03 (0.01–0.06)	0.16 (0.02–0.38)	0.10 (0.03–0.16)
CD16+CD56	0.05 (0.02–0.11)	0.06 (0.04–0.18)	0.04 (0.02–0.06)
CVID EUROClass			
smB+21^{Lo}	5	3$^{\#}$	
smB+21^{norm}	1		1
smB-21^{Lo}		2	3
B-	1		

Data are presented as median (interquartile range). MMF: mycophenolate mofetil; CVID: common variable immunodeficiency disorder. $^{\#}$: two patients were also in the acute steroid group.

time between the evaluated PFTs was 214±77 days. There was no significant change in the FVC% and FEV_1% between pre- and post-treatment with acute corticosteroids (median change in FVC=6%, p=0.09, and FEV_1=0.10%, p=0.92). However, there were significant improvements in D_{LCO}% and K_{CO}% (median change in D_{LCO}%=7%, p=0.04, and K_{CO}%=13%, p=0.02) (figure 1a). Taking a >10% change in D_{LCO} as a clinically significant improvement, 43% of patients responded to acute corticosteroid treatment. Additional information about treatment response is presented in table 3.

Two patients weaned the prednisone dose to ⩽6 mg and remained in remission for a mean of 5.3 years. One patient developed a severe lung infection 6 months after initiating weaning (17.5 mg), causing the patient to become oxygen dependent and unable to perform further gas transfer tests to evaluate GLILD. However, this patient did not receive further immunosuppressant treatment. One patient had immunosuppression escalated for reasons other than GLILD. Patients who were re-treated with another course of corticosteroid and/or second-line agents for GLILD were considered as relapsed. By this definition, three patients (42%) relapsed after a median time of 111 days when receiving a mean maintenance prednisone dose of 4 mg.

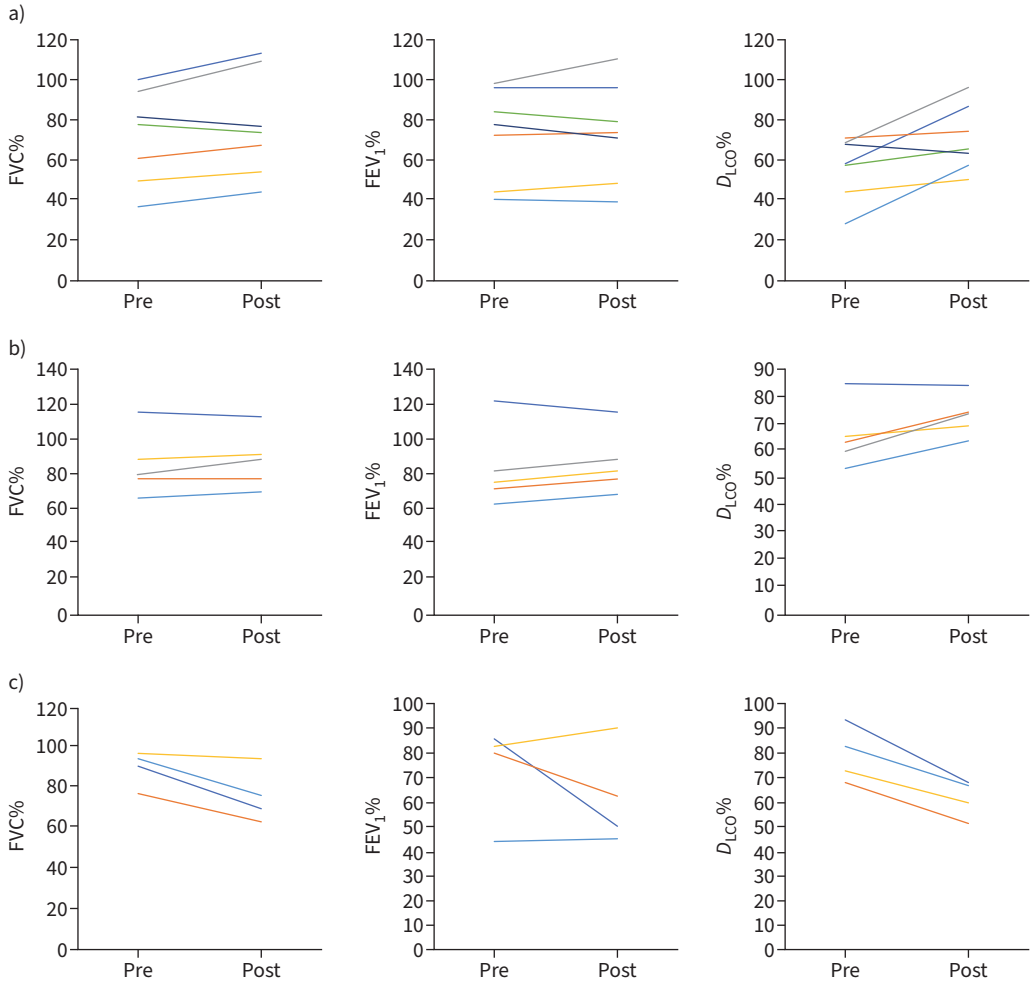

FIGURE 1 Pulmonary function test results before and after immunosuppressive therapy. a) Received acute steroid to induce remission, b) received mycophenolate mofetil with or without corticosteroids to maintain remission and c) received no treatment other than immunoglobulin replacement therapy. Each line represents an individual patient. FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide.

TABLE 3 Medications used for treatment of granulomatous lymphocytic interstitial lung disease and lung function results before and after treatment

Group	Time months	PFT	Before treatment	After treatment	p-value
Acute corticosteroid 0.5–1 mg·kg^{-1} daily	3.8	FVC%	77 (50–95)	74 (54–110)	0.09
		FEV_1%	77 (42–96)	73 (48–96)	0.92
		D_{LCO}%	59 (43–69)	66 (57–86)	0.04
Mycophenolate mofetil 500–1000 mg twice a day	46	FVC%	79 (71–102)	89 (72–102)	0.35
		FEV_1%	74 (66–100)	81 (73–102)	0.08
		D_{LCO}%	63 (55–75)	72 (67–79)	0.04
Immunoglobulin replacement only 400–800 mg·kg^{-1} 3-weekly	94	FVC%	92 (80–95)	72 (65–89)	#
		FEV_1%	82 (53–85)	57 (46–83)	#
		D_{LCO}%	77 (69–90)	64 (54–68)	#

Data are presented as median (interquartile range), unless otherwise stated. PFT: pulmonary function test; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide. #: no significant difference compared with pre-treatment period due to small group numbers.

Lung function response to mycophenolate mofetil with/without corticosteroid

Five patients were treated with long-term MMF (36%) intended to maintain remission. The mean time between GLILD diagnosis and MMF initiation was 1.2±1.1 years. Two had relapsed after multiple courses of acute steroids and had been included in the section "Lung function response to acute corticosteroids". Three patients started MMF with acute corticosteroids, one had MMF added to background steroids and one had MMF alone. The mean daily prednisone dose at MMF initiation was 37±32 mg. The mean duration of MMF use was 1277 days (=3.5 years; SD 917 days) with a mean MMF dose of 1250±250 mg·day^{-1}. One patient discontinued the treatment after 10 months due to recurrent gum inflammation. All four patients on steroids successfully weaned the prednisone dose over 12 months on MMF such that two patients required no corticosteroid, one remained on 5 mg and one remained on 7.5 mg·day^{-1}.

The mean time between the evaluated PFTs was 1306 days (=3.6 years; SD 901 days). Chronic treatment with MMF resulted in no change in FVC% and FEV_1% (median change in FVC=3%, p=0.35, and FEV_1=6%, p=0.08). However, there was a significant increase in D_{LCO}% and K_{CO}% (median change in each of D_{LCO}% and K_{CO}%=10%, p=0.04) (figure 1b) over this period of 3.6 years, equivalent to 2.7% per year in each test. 60% of patients responded in terms of a change in D_{LCO} of >10%; these were all patients who started MMF with acute steroids (40, 50 and 60 mg). More information about treatment results is presented in table 3.

No immunosuppressant treatment

Our records showed four GLILD patients who never received immunosuppression therapy. Among these patients, we found a significant decline in spirometry results over a mean time of 2705 days (7.5 years; SD 917 days). The median decline in the FVC% and FEV_1% were 15% and 7%, equivalent to 2% and 1% per year, respectively. The gas transfer was also affected in this group, and the D_{LCO}% reduced by a mean of 15%, equivalent to 2% per year (figure 1c).

Discussion

We report the first long-term, longitudinal study of lung function in a complete single-centre cohort with GLILD considering three treatment scenarios: background immunoglobulin replacement only, acute use of corticosteroids intended to achieve remission and chronic use of MMF with weaning corticosteroids intended to maintain remission (figure 1). The key findings of our research are: 1) the efficacy of high-dose steroids in achieving remission (in 43%, based on >10% change in D_{LCO}); 2) relapse (or other complications) commonly occurs when weaning corticosteroids; 3) MMF was associated with improved lung function and disease stabilisation permitting corticosteroid weaning; and 4) no treatment other then IgRT leads to a significant decline in lung function over time implying that treatment at an early stage may be better than watchful waiting. These results add to the existing literature on treatment of GLILD [5].

Corticosteroids were suggested as first-line treatment in the BLF/UKPIN Consensus Statement [4]. The effectiveness of glucocorticoid monotherapy varies from one study to another, as assessed by clinical symptoms, lung function and radiological findings. A retrospective study by Boursiquot *et al.* [7] evaluated the efficacy of immunosuppressive drugs in CVID patients with granulomatous disease. They reported 13 patients treated with glucocorticoids at an initial dose of 30–60 $mg \cdot day^{-1}$ for a median of 18 months, of whom complete remission occurred in only three patients. Moreover, a recent systematic review evaluated all available studies and reported that 57% of GLILD patients treated with glucocorticoids failed to remain in remission upon tapering the dose [5]. Our results are consistent with this, as we found that despite the improvement in lung function in >40% patients treated with acute corticosteroids, relapse occurred when the treatment was tapered in five out of seven patients. This resulted in repeating the course of treatment or using second-line treatments.

MMF is an immunomodulatory agent that inhibits the proliferation of lymphocytes [8]. MMF is used to treat several renal and autoimmune disorders, including immune thrombocytopenia [9]. In addition, positive effects of MMF on lung function have been reported in treating connective tissue disease-associated interstitial lung disease and chronic hypersensitivity pneumonitis [10, 11]. However, there are limited reports about the use of MMF as a monotherapy or in conjunction with corticosteroids for GLILD. Tashtoush *et al.* [12] reported a case of a patient with GLILD where 3 months of glucocorticoids induced remission and MMF helped to maintain the improvement for a further 9 months. Additionally, Bucciol *et al.* [13] reported three paediatric patients diagnosed with CVID and GLILD. MMF was used to treat cytopenias after the failure of glucocorticoids. The treatment improved the cytopenias and also appeared to stabilise the lung disease, but the duration of this benefit was not clear. Our results support these findings. We found that MMF enabled successful weaning of corticosteroids with no relapse. Moreover, MMF helped maintain spirometry and was associated with improvement in gas transfer over a mean of 4 years. Considering the long-term adverse effects of corticosteroids, including on bone density and metabolism, a strategy employing MMF either as monotherapy or with a lower dose of glucocorticoids should, for most patients, result in clinical stability and/or improvement while minimising side-effects. The drug was well tolerated (only one in five patients discontinued the drug).

The superiority of first-line treatment over watchful waiting was one of the top-ranked questions in a recent research prioritisation exercise in GLILD [14]. We are the first complete, single-centre cohort reporting the change in lung function over time for GLILD patients who were not receiving immunosuppression treatment. Our results showed a substantial decline in lung function over a mean time of 8 years. This highlights the importance of considering early treatment if initial tests suggest progressive lung function decline.

This study has several limitations. We are the largest UK centre for GLILD yet still the number of patients included in this study was small, which reduced statistical power. Here, we only consider change in lung function. Changes in symptoms and imaging would also be important to consider in assessing the benefits of treatment. Patients had different treatment patterns, and the evaluation of treatment efficacy did not take into consideration the baseline severity of their lung disease. The choice of treatments was not randomised, and the control group may have had particular reasons why active immunosuppression was not used. We are not able to comment on how any previous treatment might have impacted changes in relation to the treatment under study.

In conclusion, this retrospective study of 14 patients with CVID and GLILD illustrates the effect of different treatment scenarios. The use of MMF-based maintenance demonstrates long-term effectiveness in patients with GLILD, permitting weaning of corticosteroids, and suggests that treatment after initial response to high-dose corticosteroids could include MMF. A delay in initiating treatment could lead to disease progression. Additional research is needed to determine the best treatment options for GLILD patients.

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Availability of data and material: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Author contributions: H.M. Bintalib, D.M. Lowe, S.O. Burns and J.R. Hurst contributed to the study conception and design. Material preparation and data collection were performed by H.M. Bintalib, G. Mancuso and G. Gkrepi. Initial analysis, interpretation and evaluation of data were led by H.M. Bintalib and J.R. Hurst. The first draft of the manuscript was written by H.M. Bintalib and all authors commented on subsequent versions of the manuscript. All authors read and approved the final manuscript.

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