Efficacy and safety of enteric-coated mycophenolate sodium in combination with two glucocorticoid regimens for the treatment of active lupus nephritis

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Mycophenolic acid, in combination with glucocorticoids, has been shown in a series of trials to be safe and effective for treatment of lupus nephritis. Regimens that permit glucocorticoid dose reduction without loss of efficacy would be advantageous. MyLupus was a 24-week, multicentre, open-label, study in patients with active proliferative lupus nephritis treated with enteric-coated mycophenolate sodium (EC-MPS), randomized to standard-dose (n = 42) or reduced-dose (n = 39) glucocorticoids. Complete response at week 24, the primary endpoint, was achieved in 19.8% (16/81) of patients (19.0% standard-dose, 20.5% reduced-dose; lower limit of 97.5% CI for the difference /C0 15.9%, p = 0.098, i.e. non-inferiority was not shown). Partial response occurred in 42.0% of patients (34/81). From baseline to week 24, the mean global British Isles Lupus Assessment Group (BILAG) score decreased from 14.0 /C6 5.4 to 5.0 /C6 3.8 (p < 0.001). The incidence of adverse events was 80.2% (65/81), most frequently gastrointestinal complications (31/81, 38.3%). Infections were reported in 57.1% and 35.9% of standard- and reduced-dose glucocorticoid patients, respectively (p = 0.056), with herpes zoster in 16.7% and 0% (p = 0.012). Three patients discontinued study medication due to adverse events. This exploratory study suggests that EC-MPS may facilitate glucocorticoid reduction without loss of efficacy in patients with active lupus nephritis, but results require confirmation in a controlled, longer-term study versus the current standard of care.

Key words: active; corticosteroids; EC-MPS; lupus; mycophenolic acid; myfortic

Introduction

Lupus nephritis occurs in approximately 40–50% of adults with systemic lupus erythematosus (SLE).1–3 It can progress to end-stage renal disease4 with an associated increase in mortality.5 Despite the high toll of lupus nephritis and progress in understanding of its pathogenesis, current treatment options remain limited. The introduction of combined therapy using cyclophosphamide and glucocorticoids improved prognosis compared with glucocorticoids alone,6 but both short- and long-term toxicity of the combination regimen are considerable. Although sequential protocols have been developed which avoid long-term exposure to high-dose cyclophosphamide,7–9 therapies that avoid the need for short-term induction with cyclophosphamide would be highly beneficial. Moreover, extended high-dose glucocorticoid therapy should be avoided due to adverse events that can be clinically important, such as cardiovascular or infectious complications, or distressing for the patient. The development of regimens that permit glucocorticoid dose reduction without loss of efficacy would be advantageous.10

A series of trials have suggested that mycophenolic acid (MPA) may be a safe and effective alternative to cyclophosphamide in lupus nephritis for achieving renal response,11–19 including studies in patients with severe disease,12,13,15 and during the

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Enteric-coated mycophenolate sodium (EC-MPS) is an advanced formulation in which release of MPA is delayed until it reaches the small intestine without affecting the extent of drug exposure compared with the original mycophenolate mofetil (MMF) formulation. In lupus nephritis, initial prospective and retrospective data have suggested a potential role for EC-MPS in the treatment of active lupus nephritis or for cyclophosphamide-resistant cases.

The 24-week MyLupus study was designed to evaluate the efficacy of EC-MPS for achieving response when administered in combination with either a standard-dose or reduced-dose glucocorticoid protocol in patients with lupus nephritis. The primary objective was to explore the non-inferior efficacy of EC-MPS with reduced-dose corticosteroids versus a standard-dose regimen based on the proportion of patients in complete remission after 24 weeks of treatment. This exploratory, open-label study was undertaken to provide a basis for future controlled clinical trials of MPA in lupus nephritis.

Methods

Study design and conduct

This was a 24-week, randomized, multicentre, open-label, parallel-group study in which patients with SLE presenting with a proliferative lupus nephritis flare were treated with EC-MPS in combination with either a standard-dose or reduced-dose regimen of glucocorticoids. Patients were recruited and managed at 19 nephrology, rheumatology, internal medicine or immunology centres in 9 countries (France, Germany, Italy, Spain, United Kingdom, Hungary, Greece, Colombia and Taiwan). The trial was carried out in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice and the Declaration of Helsinki following approval from local institutional review boards. All patients provided written informed consent.

Study population

Male and female patients aged ≥18 years were eligible to enter the study if they met the following criteria: (i) diagnosed with SLE, defined as meeting at least 4 classification criteria of the American College of Rheumatology (ACR); (ii) presence of proliferative lupus nephritis classified as International Society of Nephrology/Renal Pathology Society (ISN/RPS) class III or IV; (iii) renal biopsy performed within the previous 24 months prior to study entry; (iv) proteinuria defined as urine protein:creatinine ratio >0.5 at screening and baseline; and (v) clinical activity defined by one or more of the following: serum creatinine >1 mg/dL; microscopic haematuria (≥5 red blood cells/high power field) and presence of cellular casts. Key exclusion criteria were calculated creatinine clearance (Cockcroft–Gault) <30 mL/min and receipt of a bolus intravenous glucocorticoids, oral or intravenous cyclophosphamide or MMF during the previous 3 months or antibody therapy within the previous 6 months.

Intervention

Following a two-week screening period, patients were randomized at baseline in a 1:1 ratio to one of two glucocorticoid dosing groups. A randomization list was generated using a validated system with corresponding treatment allocation scratch cards being distributed to participating centres for investigators to remove the cover and reveal the treatment allocation for the patient assigned to the randomization number shown on the card. Starting on day 1, all patients received a bolus of 0.5 mg/day intravenous methylprednisolone for 3 days before oral glucocorticoid therapy started on day 4. In the standard-dose group, the oral dose of glucocorticoids during days 4–14 was 45 mg/day for patients weighing ≤45 kg, 50 mg/day for patients weighing >45 kg and ≤55 kg, 60 mg/day for patients weighing >55 kg and ≤65 kg, and 70 mg/day for patients weighing >65 kg. The dose subsequently declined based on a pre-specified weight-adjusted schedule to 5 mg/day by week 24 in patients weighing ≤65 kg and 10 mg/day in patients weighing >65 kg. In the reduced-dose group, the initial dose was half that of the standard-dose group: 22.5 mg/day for patients ≤45 kg, 25 mg/day for patients >45 kg and ≤55 kg, 30 mg/day for patients >55 kg and ≤65 kg, and 35 mg/day for patients >65 kg. The dose was then reduced according to patient weight to 2.5 mg/day in patients weighing ≤65 kg and 5 mg/day in those weighing >65 kg.

All patients received EC-MPS at a dose of 1440 mg/day (720 mg bid or in three divided doses) for two weeks and 2160 mg/day thereafter (1080 mg bid or three doses of 720 mg).

Study endpoints

The primary efficacy endpoint was the proportion of patients showing complete response at week 24. Complete response was defined as urine...
protein:creatinine ratio <0.5 with normalized urine sediment and serum creatinine within 10% of normal value. Secondary efficacy variables included (a) the proportion of patients showing complete response at 12 weeks; (b) the proportion of patients showing partial response at 12 and 24 weeks, with partial response defined as a reduction in urine protein:creatinine ratio of ≥50% compared with baseline, and serum creatinine improved or stable (i.e. within 10% of baseline value); (c) the proportion of patients with mild, or with moderate-to-severe SLE flare at 12 and 24 weeks (a mild SLE flare was diagnosed if lupus activity increased after partial or complete response, defined as the presence of 1 or 2 BILAG27 B scores and no A scores and intention by the investigator to increase the glucocorticoid dose; a moderate to severe SLE flare was diagnosed if increased lupus activity after partial or complete response resulted in 1 BILAG A score or ≥3 BILAG B scores); (d) disease activity as measured by the global BILAG score28 and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)29 at 4, 12 and 24 weeks; (e) the cumulative and daily dose of glucocorticoids at 12 and 24 weeks; (f) renal function as assessed by serum creatinine, creatinine clearance (Cockcroft–Gault),30 estimated glomerular filtration rate, Modification of Diet in Renal Disease formula (GFR, MDRD formula)31 and urine protein:creatinine ratio. Safety variables included adverse events, severe adverse events and study drug discontinuation.

Evaluation

Following screening, study visits took place at baseline (day 1) and at weeks 2, 4, 8, 12 and 24. Patients who discontinued the study prematurely were to complete the week 24 study visit where possible. The BILAG and SLEDAI indices were completed at baseline, weeks 4, 12 and 24. For each of the eight organs/systems scored on a decreasing severity scale of A to E in the BILAG test (e.g. ‘A’ denotes disease thought to be sufficiently active to require disease modifying treatment; ‘E’ indicates that the system or organ has never been involved), a global BILAG score was created by the following assignments: A = 9, B = 3, C = 1, D/E = 0. The possible BILAG global score therefore ranged for each patient from 0 to 72.

Serum creatinine was measured at a central laboratory. Adverse events and serious adverse events were recorded at each visit. The key criteria for serious adverse events, including infections, were that they were fatal or life-threatening, resulted in persistent or significant disability/incapacity, required hospitalization or prolongation of hospitalization, or were regarded as medically significant.

Statistical analysis

The primary efficacy variable was the proportion of patients showing complete response at 24 weeks. For this exploratory study, the sample size calculation assumed that 22.5% of patients in both treatment groups would show complete response, based on published data.10 Using a non-inferiority margin of 10%, a sample size of 80 patients would have 19% power to demonstrate non-inferiority of the reduced-dose glucocorticoid group to the standard-dose group using a one-sided 97.5% confidence interval (CI) approach. Sample sizes were calculated using nQuery Advisor 5.0 software.

The proportion of patients experiencing the primary efficacy endpoint was compared between treatment groups using the Chi Square test. The one-sided 97.5% CI for differences in proportions between two groups was calculated using the Z-test statistic. Analysis of all secondary endpoints was exploratory. Between-group differences in change from baseline for disease indices and renal function were compared using the Wilcoxon rank sum test.

The intention-to-treat (ITT) population comprised all randomized patients who received at least one dose of study drug and provided at least one post-baseline safety assessment of the primary efficacy variable. All primary and secondary efficacy analyses were based on the ITT population. The safety population represented all randomized patients in whom at least one post-baseline safety assessment was undertaken.

A planned interim analysis was undertaken when 50% of randomized patients (n = 40) had completed 12 weeks of the study to allow for early detection of any safety issues. Results of the interim analysis were provided to the Data Monitoring Board to support the risk/benefit assessment.

Statistical analyses were performed using SAS software (version 9.2).

Results

Patient population

A total of 81 patients were randomized (42 standard-dose glucocorticoids, 39 reduced-dose glucocorticoids) and formed the ITT and safety populations. Of these, 74 (91.4%) completed the
24-week study (Figure 1). Two patients in the standard-dose group died before completing the study, and a further standard-dose patient completed the study but discontinued study medication prematurely. In the reduced-dose arm, four patients discontinued (two due to adverse events, one due to unsatisfactory therapeutic effect, and one due to administrative problems). The first patient visit took place in February 2007, and the final patient visit in November 2009. Demographics and baseline characteristics are summarized in Table 1. The mean age of the study population was 33.1 years and the majority of patients were female (82.2%), with a mean time since diagnosis of 56.9 months. The majority of patients had a diagnosis of ISN/RPS class IV at baseline. Seven patients (2 standard-dose, 5 reduced-dose) did not have urine protein:creatinine ratio >0.5 at screening and baseline and were included against protocol.

**Study medication**

All patients continued glucocorticoid treatment while remaining in the 24-week study. The mean (± SD) cumulative dose of prednisone equivalents to week 24 was 7111 ± 1292 mg (114 ± 15 mg/kg) in the standard-dose group and 4630 ± 1021 mg (73 ± 18 mg/kg) in the reduced-dose arm (p <0.001). The mean daily dose of prednisone equivalents in the standard-dose and reduced-dose groups was 115 ± 8 mg/day (1.9 ± 0.2 mg/kg/day) and 93 ± 35 mg/day (1.5 ± 1.7 mg/kg/day) at week 2 (p <0.001); 28 ± 10 mg/day (0.4 ± 0.1 mg/kg/day) and 15 ± 5 mg/day (0.2 ± 0.1 mg/kg/day) at week 12 (p <0.001); and 11 ± 5 mg/day (0.2 ± 0.1 mg/kg/day) and 7 ± 5 mg/day (0.1 ± 0.1 mg/kg/day) at week 24 (p <0.001) respectively (Figure 2). The mean dose of EC-MPS was 1984 ± 192 mg/day to week 12, and 2002 ± 204 to week 24.

**Response rate**

The primary efficacy endpoint, complete response at week 24, occurred in 19.8% (16/81) of patients overall. Complete response was achieved in 19.0% (8/42) of standard-dose patients and 20.5% (8/39) (p = 0.87, Chi squared) of reduced-dose patients but non-inferiority could not be shown (lower limit of the 97.5% CI for the difference −15.9%, p = 0.098) (Table 2). Partial response occurred in 42.0% of patients (34/81) at week 24. In total, the proportion of patients with complete or partial response at week 24 was 61.7% (50/81), (66.7% [28/42] standard-dose patients and 56.4% [22/39] reduced-dose patients).

**SLE activity**

From baseline to week 24, the mean global BILAG score decreased from 14.0 ± 5.4 to 5.0 ± 3.8 (p <0.001); mean SLEDAI score decreased from 16.2 ± 6.9 to 6.2 ± 5.1 (p <0.001). Only one patient, in the standard-dose group, experienced an SLE flare. This was graded moderate-to-severe. There were no significant differences between treatment

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**Figure 1** Patient disposition. ITT, intention to treat.
groups in the improvement in activity index scores from baseline to month 24 (Figure 3) or at any time point (data not shown).

Median (range) values at baseline and month 24 were 97 (2–561) and 39 (0–301) kIU/L for anti-dsDNA, 0.7 (0.3–167) and 1.0 (0.5–189) g/L for C3, and 95 (10–464) and 181 (12–444) g/L for C4, respectively. There were no differences between treatment groups for values of anti-dsDNA, C3 or C4 complement levels at baseline or week 24.
Renal function

Mean GFR and urine protein:creatinine ratio showed significant improvements from baseline to month 24; other renal function parameters showed no significant differences (Table 3). The change from baseline to month 24 was similar in both treatment groups for all renal function parameters other than a significantly greater improvement for urine protein:creatinine ratio in the standard-dose group (Table 3).

Safety

Adverse events were reported in 80.2% (65/81) patients (Table 4). Gastrointestinal (GI) symptoms were the most frequent type of adverse event ($n = 31$, 38.3%). The incidence of adverse events with a suspected relation to study drug was 41.9% ($n = 34$), including GI disorders in 17.3% of patients ($n = 14$). Infections occurred in 38 patients (46.9%), comprising 24 (57.1%) and 14 (35.9%) patients in the standard-dose and
reduced-dose groups, respectively ($p=0.056$, chi-square test). The most frequent infection was herpes zoster, which was reported in seven standard-dose patients and no reduced-dose patients ($p=0.012$, Fisher exact test).

Serious adverse events occurred in 12 patients (14.8%) (19.0% [8/42] standard-dose patients, 10.3% [4/39] reduced-dose patients, $p=0.266$ [chi-square test]). No serious adverse event was reported in more than one patient other than hypertension (one patient in each group). Two standard-dose patients experienced three serious GI adverse events: diarrhoea, vomiting and acute pancreatitis. Five patients experienced serious infections, comprising five infections in standard-dose patients (cytomegalovirus, Epstein–Barr virus, gastroenteritis, herpes zoster and sinusitis) and one infection in a reduced-dose patient (gastroenteritis). One patient in the standard-dose group discontinued study medication due to adverse events (gastroenteritis). One death occurred following severe respiratory distress, and no relation with study medication was suspected. The other was due to multiorgan failure in a patient with acute pancreatitis; concomitant acute cytomegalovirus and Epstein–Barr infections that were suspected to have a relationship with study medication.

Discussion

In this prospective study of EC-MPS for the management of active lupus nephritis, EC-MPS in combination with glucocorticoids achieved complete or partial response in over 60% of patients by week 24. The combination was well-tolerated, with the mean dose maintained close to the recommended value and few patients discontinuing study medication due to adverse events (~6%). Despite a 50% difference in cumulative steroid dose over the 24-week study, the rate of complete response was almost identical in the standard-dose and reduced-dose glucocorticoids cohorts, although partial response was numerically more frequent with the standard regimen. Serious infections occurred more frequently in the cohort randomized to standard glucocorticoid dosing.

While cross-study comparisons must necessarily be regarded with caution, the rates of complete and partial response observed in the current study (19.8% and 42.0%) and in a 24-week randomized study of MMF with similar MPA exposure and glucocorticoids (22.5% and 29.5%) were at least comparable. Definitions for complete and partial response were similar in the two trials. In another recent 24-week randomized study, in which MMF was compared to cyclophosphamide, response was defined as a decrease in urine...
protein:creatinine ratio to <3 if baseline value was ≥3, or by ≥50% in patients with a baseline value <3, together with stabilization (±25%) or improvement in serum creatinine at 24 weeks. Using that slightly wider definition, response was achieved in 56% of MMF-treated patients. It should be noted that baseline renal function according to various markers was inferior in these two studies compared with our own population. The standard-dose glucocorticoids regimen in our study was typical of that used elsewhere in patients with active lupus nephritis receiving MMF induction such that the reduced-dose group in the current study represented a marked decrease from normal glucocorticoid exposure in MMF-treated patients. The proportion of patients achieving complete response by week 24 was similar in the standard-dose and reduced-dose glucocorticoid arms, but this exploratory study had only a 19% power to detect non-inferiority based on a margin of 10% and, indeed, non-inferiority was not shown. It is a potential concern, however, that the rate of partial response was numerically, although not statistically lower, in the reduced-dose group. Encouragingly, though, only one patient (in the standard-dose group) experienced an SLE flare by week 24. Decreases in BILAG and SLEDAI suggested that there was a clinically meaningful improvement in disease activity over the 24-week study.

While the incidence of adverse events was virtually identical in the standard-dose and reduced-dose arms, there was a slightly lower rate of serious adverse events among patients randomized to the reduced glucocorticoid regimen (~10% versus 19% with the standard regimen), and five out of the six serious infections occurred in patients given standard glucocorticoid doses. Overall, the incidence of infection was noticeably higher in the standard-dose glucocorticoid arm. GI complications were also more frequent with standard glucocorticoid exposure, which if confirmed in a larger study would not be unexpected since GI toxicity is a well-recognized effect of chronic glucocorticoid therapy.

GFR improved during the 24-week study to an extent that was clinically relevant. There was a significantly greater improvement in the urine protein:creatinine ratio in the standard-dose group versus the reduced-dose group, but this difference was not considered to be clinically relevant. Mean values for all renal function parameters were within normal range.

This relatively small exploratory study was not adequately powered to prove non-inferiority of the
two treatment arms. Moreover, the open-label design of the study risked the introduction of bias, but this may have been lessened by the fact that the novel therapy, EC-MPS, was the same in both treatment arms. In conclusion, the results of this exploratory study suggest that a regimen of EC-MPS with glucocorticoids may be a viable therapy for active lupus nephritis. It also appears possible that glucocorticoid dosing could be reduced in the presence of concomitant EC-MPS without loss of efficacy for the management of lupus nephritis flare. These findings, however, are preliminary and the efficacy of EC-MPS requires confirmation in a controlled, longer-term study against the current standard of care.

Acknowledgements

With grateful thanks to Reto Brambilla, Anne-Claire Marrast, Yolandi Joubert and Isabelle Indermuehle of Novartis; and to Caroline Dunstall for editorial support.

Funding

The study was funded by Novartis Pharma AG.

Conflicts of interest

IB and GA have received research funding from Novartis. FH has received research funding and travel grants from Novartis, and is a member of a Novartis Advisory Board. IB is a member of a Novartis Advisory Board. DJ has received research grant support from Vifor Pharma, and research grants support and lecture fees from Roche. HP and PB are employees of Novartis Pharma AG. The other authors have no conflicts of interest to declare.

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