RESEARCH

Glucocorticoid therapy as first-line treatment in primary hypophysitis: a systematic review and individual patient data meta-analysis

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Abstract

Objectives: High-dose glucocorticoids are associated with improved recovery of deficits in primary autoimmune hypophysitis (PAH), but optimal dosing, route, and duration are unclear.

Design: We reviewed literature for first-line glucocorticoid treatment in PAH until December 2021 and performed an individual patient data meta-analysis to analyze clinical, hormonal, and radiological outcomes with respect to route, dose, and duration (<6.5 vs 6.5–12 vs >12 weeks) of glucocorticoid treatment according to disease severity.

Results: A total of 153 PAH patients from 83 publications were included. The median age at presentation was 41 (32.5–48) years with a female preponderance (70.3%). Visual field recovery was significantly better with i.v. (91.7%) as compared to oral (54.5%) route and high dose (100%) and very high dose (90.9%) as compared to medium dose (20%) of glucocorticoids. Corticotroph axis recovery was greater in i.v. (54.8% vs 28.1% oral, $P = 0.033$) route and increasing glucocorticoid dose group (0% vs 38.1% vs 57.1%), attaining statistical significance ($P = 0.012$) with very high-dose. A longer duration of treatment (>6.5 weeks) was associated with better corticotroph and thyrotroph recovery. The need for rescue therapy was lower with i.v. route (38% vs 17.5%, $P = 0.012$) and with increasing glucocorticoid doses (53.3% vs 34.3% vs 17.3%, $P = 0.016$). In severe disease, visual field and corticotroph axis recovery were significantly higher with i.v. route and very high-dose steroids. The adverse effects of glucocorticoids were independent of dose and duration of treatment.

Conclusions: Very high-dose glucocorticoids by i.v. route and cumulative longer duration (>6.5 weeks) lead to better outcomes and could be considered as first-line treatment of severe PAH cases.

Key Words

- primary autoimmune hypophysitis
- very high-dose glucocorticoids
- duration of treatment
- need for rescue therapy
- intravenous glucocorticoids

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Introduction

Hypophysitis is the general term used to describe any form of sellar and/or suprasellar inflammation that leads to structural changes in the hypothalamic–pituitary axis and varying degrees of anterior and/or posterior pituitary hormonal deficiencies. Though several secondary etiologies viz., autoimmune, infectious, infiltrative, neoplastic, and drug-induced forms have been described, primary autoimmune hypophysitis (PAH) remains common (1).

The goals of PAH treatment include the reversal of mass effect-related neurological manifestations,

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replacement of deficient hormones, and preservation/recovery of pituitary hormonal function (2). There is a lack of consensus on the optimal strategy for the treatment of hypophysitis because of the rarity of the disease, heterogeneity in clinical presentation and natural history of the disease, and lack of randomized clinical trials comparing the efficacy of different treatment modalities (3). Choosing a first-line treatment modality depends on the severity of the presentation and stage of the disease. The traditional approach to treatment, i.e. surgery, is now limited only to obtaining tissue for histopathological diagnosis or in the event of progression/relapse to immunomodulatory therapies (1). The remaining treatment options include observation or glucocorticoid therapy and each of them can be used as the primary treatment based on clinical scenario. A recent meta-analysis concluded that patients with milder presentation be observed, reserving supraphysiological dose of glucocorticoid therapy for those with severe or progressive neurologic deficits. Anterior pituitary hormonal (APH) recovery rate was highest with glucocorticoids (45.5%) when compared to surgery (14%) and observation (21%) but with a disadvantage of a higher proportion of patients having disease progression or relapse (4). In the former study, treatment with any supraphysiological dose of glucocorticoids was considered a high dose; however, the optimal initiating dose, route of administration, and duration of treatment are not known.

In this study, we report an individual patient data meta-analysis (IPD-MA) of the published English literature on PAH cases treated with glucocorticoids as a first-line modality to delineate the impact of the route, dose, and duration of glucocorticoid treatment on the clinical, hormonal, radiological outcomes.

Methods

This retrospective study was conducted after obtaining approval from Institutional Ethics Committee III (EC/OA-68/2020). We used Population–Intervention–Comparison–Outcomes (PICO) model for formulating the study.

Literature search strategy for systematic review and meta-analysis

We reviewed the published English literature for glucocorticoid treatment in primary hypophysitis in PubMed and EMBASE, until December 2021 (Fig. 1). To increase the sensitivity of our search, we combined variants of words '((hypophysitis) OR (infundibulo-neurohypophysitis) OR (adenohypophysitis) OR (panhypophysitis)) AND ((steroid) OR (glucocorticoid) OR (corticoids) OR (predniso*) OR (corticoster*) OR (methylprednisolone) OR (conservatively) OR (conservative))' as keywords with 'humans' and 'English' language filters. We further manually reviewed the bibliographies of retrieved studies to include cases not otherwise identified by an electronic database search. The meta-analysis and systematic review were performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The PICO model was applied to formulating the research question.

Selection criteria

Patients with PAH, in whom a therapeutic dose of glucocorticoids (≥10 mg/day) was used as a first-line treatment modality, were included in the study. In the larger series, those patients having secondary hypophysitis or those treated with glucocorticoids as a second-line modality were excluded. Cases with limited surgery/biopsy were included. Overall, we reviewed 153 patients from 83 publications on glucocorticoid treatment in primary hypophysitis previously reported in the literature. The diagnosis was based on histopathological and clinico-radiological features in 49 and 104 patients, respectively. This systematic review included 76 case reports, 2 prospective studies, and 5 retrospective studies (Supplementary file, see section on supplementary materials given at the end of this article).

Data extraction

Two authors, BK and RS, independently screened the searched citations for relevant articles. The following information was extracted from each article: demographic details, duration of symptoms, baseline and follow-up clinical, hormonal, and radiological data, and glucocorticoid regimen details (including dose, route, duration, and adverse events if any). The patients were divided into two groups, the oral steroid group (OSG) and the i.v. glucocorticoid group (IVSG) based on the initial route of glucocorticoid administration. To maintain homogeneity, the glucocorticoid dose was converted into a prednisolone equivalent dose using a steroid conversion calculator developed by MDCalc software (https://www.mdcalc.com/steroid-conversion-calculator#evidence) and was grouped into medium dose (≤30 mg/day), high dose (>30-100 mg/day), and very high dose (>100 mg/day) (5). Duration of glucocorticoid treatment was divided

into quartiles (<6.5 weeks (first quartile), 6.5–12 weeks (combined second and third quartiles), and >12 weeks (fourth quartile)). Cases were categorized clinically as severe (presence of any of the features namely, visual field deficit, cranial nerve palsy, severe headache, worsening neuro-ophthalmologic symptoms/signs) and mild-moderate (absence of any of the above features).

Response to treatment was divided as clinical (combination of headache, visual deficit, and cranial nerve palsy recovery), hormonal (anterior pituitary hormonal recovery, whether complete or partial), and radiological (resolution of stalk thickening and decrease in the pituitary enlargement). At follow-up, AP hormonal recovery was considered 'complete' when all the affected axes recovered, 'partial' when at least one but not all of the affected axes recovered, and 'persistent' when none of the affected axes recovered. New-onset hormonal deficit after glucocorticoid treatment was defined as 'worsening'. Similarly, the radiological outcome data were grouped into 'regression' (reversal of pituitary enlargement and stalk thickening), 'persistent' (any degree of persistent sellar enlargement and/or stalk thickening), and 'worsening' (any increase in the size of the sellar mass and/or stalk thickening) groups. Empty sella was defined as pituitary height less than 3 mm (6). The need for rescue therapy was defined as a combination of 'glucocorticoid failure' (clinical or radiological worsening after initiation of glucocorticoids), 'flare' (initial response followed by clinical or radiological recurrence during the duration of glucocorticoid therapy), and 'recurrence' (relapse of clinical or radiological features after 3 months of discontinuation of glucocorticoids).

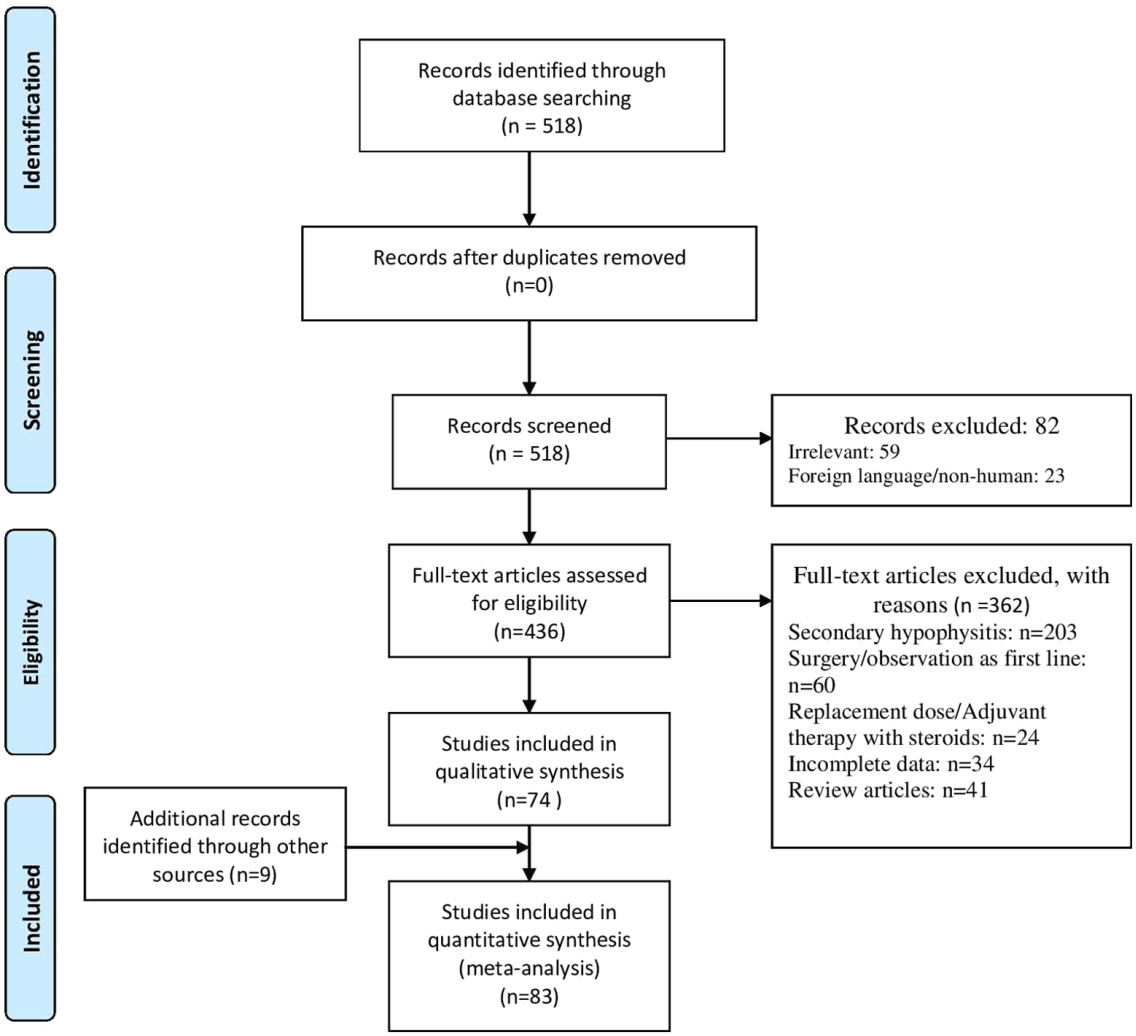

Figure 1
PRISMA flow chart for selection of articles for systematic review and individual patient data meta-analysis.

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Statistical analysis

All categorical variables were expressed in actual numbers and percentages and continuous variables as mean ± standard deviation or median and interquartile range as applicable. The categorical variables were compared using the χ^2 test, whereas continuous variables were compared using an independent *t*-test or Mann–Whitney *U* tests in normally and non-normally distributed data, respectively. A *P*-value of less than 0.05 was taken as significant. All statistical analyses were done with SPSS version 25.0 (IBM).

Results

Baseline characteristics

Baseline characteristics of the total cohort are presented in Table 1. The median age at presentation was 41 years with a female preponderance (70.1%). The median duration of symptoms onset to final diagnosis was 6 months (IQR: 2–12). The most common presentation was headache (65.5%) followed by visual defects (25.5%), whereas cranial nerve palsies were seen in 12.4% of patients. Hypogonadism and hypocortisolism were the most common APH deficiencies, seen in 61.7 and 61.1%, respectively. Diabetes insipidus (DI) was seen in 46.6% of patients. MRI showed pituitary enlargement and thickened stalk in 81.8 and 90.6% of patients, respectively. The most common histopathological subtypes were lymphocytic ($n = 35$) followed by IgG4 ($n = 9$) granulomatous ($n = 3$), mixed granulomatous-lymphocytic ($n = 1$), and xanthomatous ($n = 1$) hypophysitis. Baseline characteristics according to route (oral vs i.v.), dose (medium vs high vs very high), and duration (in weeks) (<6.5 vs 6.5–12 vs >12) of glucocorticoid treatment are represented in the Supplementary Tables 1A, B and C. Baseline features were comparable between OSG and IVSG except for a higher proportion of patients with hyposomatotropism in IVSG; a higher proportion of patients with cranial nerve palsy in medium and very high-dose glucocorticoids; a higher proportion of DI in patients who received glucocorticoids for >12 weeks.

Table 1 Baseline characteristics of the total cohort.

Demographic characteristics	
Age (years) ($n = 151$)	41 (33–48)
Female gender	89/127 (70.1)
Duration of symptoms (months) ($n = 135$)	6 (2–12)
Clinical features	
Headache	95/145 (65.5)
Visual deficits	37/145 (25.5)
Cranial nerve palsy	18/145 (12.4)
Anterior pituitary dysfunction	
Hypocortisolism	80/131 (61.1)
Hypothyroidism	75/131 (57.3)
Hypogonadotropism	79/128 (61.7)
Hyposomatotropism	42/112 (37.5)
Hypoprolactinemia	13/116 (11.2)
Hyperprolactinemia	47/115 (40.9)
Diabetes insipidus	61/131 (46.6)
Radiological features	
Pituitary enlargement	108/130 (83.1)
Thickened stalk	96/106 (90.6)
Follow-up duration (months)	18.5 (6–36)

Data are expressed as *n*/N (%) or median (interquartile range).

Table 2 Outcomes of the oral vs i.v. glucocorticoids.

Parameters	**Oral glucocorticoid** ($n = 92$)	**i.v. glucocorticoid** ($n = 61$)
Overall response (complete/partial)		
Clinical	47/60 (78.3)	34/37 (91.9)
Hormonal	30/66 (45.5)	28/42 (66.7)*
Radiological	40/55 (72.7)	34/53 (64.2)
Need for rescue therapy	30/80 (37.5)	11/61 (18.0)*
Clinical response		
Headache	47/54 (87)	33/34 (97.1)
Visual defect	12/22 (54.5)	11/12 (91.7)*
Cranial nerve palsy	3/6 (50)	7/8 (87.5)
Hormonal response		
Corticotroph	9/32 (28.1)	17/31 (54.8)*
Thyrotroph	14/36 (38.9)	10/24 (41.7)
Gonadotroph	16/37 (43.2)	12/28 (42.9)
Somatotroph	8/15 (53.3)	4/16 (25)
Prolactin normalization	14/19 (73.7)	14/16 (87.5)
Diabetes insipidus recovery	9/27 (33.3)	8/25 (32)
Radiological response		
Regression in pituitary mass	36/46 (78.3)	38/46 (82.6)
Empty sella	5/46 (10.9)	4/46 (8.7)
Resolution of stalk thickening	31/41 (75.6)	26/41 (63.4)
Need for rescue therapy		
Treatment failure	3/80 (3.8)	0/61 (0)
Flare	12/80 (15)	4/61 (6.6)
Recurrence	15/80 (18.8)	7/61 (11.5)
Follow-up duration	14.5 (6–36)	20.5 (7–46)
Adverse effects	9/28 (32.1)	17/39 (43.6)

Data are expressed as % (*n*/N) or median (interquartile range).
*$P < 0.05$ is considered significant.

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Clinical, hormonal, and radiological outcomes of glucocorticoid regimens

Route of glucocorticoid administration

The outcomes of the oral (OSG, $n=92$) vs i.v. (IVSG, $n=61$) route of glucocorticoid administration are outlined in Table 2. The clinical outcome was better in terms of higher recovery of visual field deficits (91.7% vs 54.5%, $P=0.029$) and numerically higher recovery of cranial nerve palsies in the IVSG. The overall hormonal response (45.5% vs 66.7%, $P=0.032$) and corticotroph axis recovery (54.8% vs 28.1%, $P=0.033$) were better in IVSG, whereas recovery of other AP axes was not different. A significantly higher proportion of patients achieved complete APH recovery (38.1% vs 24.2%, $P=0.05$) in the IVSG. The need for rescue therapy was lower with IVSG (38% vs 17.5%, $P=0.012$). The recovery of neither DI nor radiological parameters was different between the OSG and IVSG.

Dose of glucocorticoids

The data on the dose of glucocorticoids at initiation were available in 113 patients of which 16 received medium dose, 44 received high dose, and 53 patients received very high dose; data on treatment outcomes and follow-up are given in Table 3. The clinical response was better in high-dose (93.3% vs 55.6%, $P=0.007$) and very high-dose glucocorticoids (90.3% vs 55.6%, $P=0.017$) principally due to a higher recovery of visual field deficits in high (100% vs 20%, $P=0.002$) and very high dose (90.9% vs 20%, $P=0.006$) compared to that of medium dose. There was a progressively higher recovery of corticotroph axis recovery with increasing glucocorticoid dose group (0% vs 38.1% vs 57.1%), attaining statistical significance ($P=0.012$) with very high dose. Similarly, there was a lesser need for rescue therapy with increasing glucocorticoid doses (53.3% vs 34.3% vs 17.3%), attaining statistical significance ($P=0.005$) with very high doses and approaching the same with high doses ($P=0.071$). The outcome of other AP axes, DI, and radiological parameters was not different with varied glucocorticoid dose ranges.

Duration of glucocorticoid treatment

Of the 111 patients in whom the data were available, 28 patients received <6.5 weeks, 58 patients received 6.5–12 weeks, and 25 patients received >12 weeks of glucocorticoid treatment and the outcomes are mentioned in Table 4. The recovery of corticotroph and thyrotroph axis was significantly higher with 6.5–12 weeks and >12 weeks of glucocorticoid treatment compared to that of <6.5 weeks. Prolactin normalization was better in 6.5–12 weeks (45.5% vs 100%, $P=0.002$). On the contrary, recovery of DI was less in 6.5–12 weeks (77.8% vs 0% vs 41.2%) compared to the other two treatment duration groups.

Table 3 Outcomes of medium, high, and very high-dose glucocorticoids.

Treatment response	Medium dose ($n=16$)	High dose ($n=44$)	Very high dose ($n=53$)
Overall response (complete/partial)			
Clinical	5/9 (55.6)	28/30 (93.3)*	28/31 (90.3)$
Hormonal	7/11 (63.6)	18/30 (60)	24/36 (66.7)
Radiological	6/9 (66.7)	28/38 (73.7)	30/48 (62.5)
Clinical response			
Headache	7/9 (77.8)	26/28 (92.9)	28/29 (96.6)
Visual defect	1/5 (20)	9/9 (100)*	10/11 (90.9)$
Cranial nerve palsy	0/0 (0)	1/1 (100)	6/7 (85.7)
Hormonal response			
Corticotroph	0/6 (0)	8/21 (38.1)	16/28 (57.1)$
Thyrotroph	4/6 (66.7)	10/23 (43.5)	10/19 (52.6)
Gonadotroph	5/7 (71.4)	10/24 (41.7)	11/24 (45.8)
Somatotroph	2/2 (100)	4/11 (36.4)	4/13 (30.8)
Prolactin normalization	3/5 (60)	10/12 (83.3)	12/15 (80)
Diabetes insipidus recovery	3/6 (50)	6/20 (30)	6/20 (30)
Radiological response			
Regression in pituitary mass	7/9 (77.8)	23/28 (82.1)	34/42 (80.9)
Resolution of stalk thickening	5/8 (62.5)	21/28 (75)	24/38 (63.2)
Duration of treatment	12 (4–16)	12 (6–24)	10 (6–10)
Need for rescue therapy	8/15 (53.3)	12/35 (34.3)	9/52 (17.3)$
Adverse effects	2/2 (100)	7/22 (31.8)	15/36 (41.7)

Data are expressed as % (*n*/N) or median (interquartile range).
*P value of <0.05 between medium and high-dose glucocorticoids; #P value of <0.05 between high and very high-dose glucocorticoids; $$P$ value of <0.05 between medium and very high-dose glucocorticoids.

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Table 4 Outcomes of varied duration of treatment with glucocorticoids.

Parameters	Duration of treatment		
	<6.5 weeks ($n = 28$)	6.5–12 weeks ($n = 58$)	(>12 weeks) ($n = 25$)
Overall response (complete/partial)			
Clinical	15/18 (83.3)	35/41 (85.4)	11/15 (73.3)
Hormonal	10/19 (52.6)	25/49 (51.0)	12/18 (66.7)
Radiological	13/22 (59.1)	23/36 (63.9)	15/22 (68.2)
Clinical response			
Headache	14/16 (87.5)	38/41 (92.7)	12/14 (85.7)
Visual defect	3/5 (60)	7/12 (58.3)	1/ 4 (25)
Cranial nerve palsy	2/2 (100)	5/8 (62.5)	0/0 (0)
Hormonal response			
Corticotroph	2/13 (15.4)	13/23 (56.5)*	6/12 (50)
Thyrotroph	1/8 (12.5)	11/21 (52.4)*	8/14 (57.1)$
Gonadotroph	5/12 (41.7)	11/22 (50)	8/16 (50)
Somatotroph	2/8 (25)	3/6 (50)	2/8 (25)
Prolactin normalization	5/11 (45.5)	13/13 (100)*	5/6 (83.3)
Diabetes insipidus recovery	7/9 (77.8)*	0/10 (0)	7/17 (41.2)#
Radiological response			
Regression in pituitary mass	13/19 (68.4)	27/33 (81.8)	13/15 (86.7)
Resolution of stalk thickening	9/13 (69.2)	24/34 (70.6)	13/20 (65)
Need for rescue therapy	8/28 (28.6)	15/56 (26.8)	8/18 (44.4)
Adverse effects	5/15 (33.3)	8/23 (34.8)	4/11 (36.4)

Data are expressed as % (*n*/N) or median (interquartile range).
*P value of <0.05 between 6.5 and 12 weeks duration of glucocorticoid treatment; #P value of <0.05 between 6.5–12 weeks and >12 weeks duration of glucocorticoid treatment; $$P$ value of <0.05 between <6.5 and >12 weeks duration of glucocorticoid treatment.

Glucocorticoid treatment outcomes based on disease severity at baseline

Data on the severity of PAH was available in 146 cases, of which 82 (oral, $n=51$, i.v., $n=31$) patients had mild-moderate disease and 64 (oral, $n=40$, i.v., $n=24$) patients had severe disease at diagnosis (Table 5). Among the mild-moderate cases, a higher (38.6% vs 12.9%, $P=0.015$) number of patients needed rescue therapy in the oral route compared to the i.v. route. None of the clinical, hormonal, or radiological outcomes were different, except for a higher recovery of the somatotroph axis (42.9% vs 0%, $P=0.035$) with oral glucocorticoid treatment. Among the severe cases, the clinical response was better with i.v. glucocorticoids (71.4% vs 90.9%, $P=0.08$), principally due to higher recovery of visual field deficits (91.7% vs 54.5%, $P=0.02$) compared to that of the oral route. The recovery of the corticotroph axis was higher with i.v. glucocorticoids (66.7% vs 26.7%, $P=0.041$). The comparison of varying doses and duration of glucocorticoid treatment according to baseline severity of the disease was done and the results are given in Supplementary Table 2.

Reported major adverse events

Weight gain without cushingoid features (9.5% vs 10%), cushingoid features (6.3% vs 10%), psychiatric complaints (4.3% vs 5%), diabetes mellitus (2.1% vs 5%), hypertension (1% vs 1.7%), in OSG and IVSG, respectively, were reported. The reported adverse events were independent of the initial dose and duration of glucocorticoid therapy. The data on the recovery of cushingoid features after stopping glucocorticoids are not available.

Predictors for recovery of APD

Supplementary Table 3 shows the predictors of recovery in OSG and IVSG. The presence of CDI (25% vs 64.3%, $P=0.015$) and female gender (84.3% vs 53.8%, $P=0.041$) predicted adverse and better APH recovery, respectively, in IVSG. None of the clinical or radiological features or anterior pituitary hormonal involvement predicted the outcome of glucocorticoid treatment in either group.

Discussion

In this retrospective systematic review and IPD-MA on the use of glucocorticoids in PAH, we observed a better improvement in the visual field, and corticotroph axis recovery with the i.v. route and very high-dose glucocorticoids, especially in severe disease. A longer duration of treatment (>6.5 weeks) was associated with better corticotroph and thyrotroph recovery. The reported adverse events were independent of the initial dose and

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Table 5 Outcomes of glucocorticoid treatment according to baseline severity of cases.

	Mild to moderate		Severe	
	Oral ($n = 51$)	i.v. ($n = 31$)	Oral ($n = 40$)	i.v. ($n = 24$)
Treatment regimen				
Medium dose	6/27 (22.2)	-	9/28 (32.1)[#]	1/23 (4.3)
High dose	20/27 (74.1)[*]	2/29 (6.9)	19/28 (67.9)[#]	2/23 (8.7)
Very high dose	1/27 (3.7)	27/29 (93.1)[*]	0/28 (0)	20/23 (86.9)[#]
Duration of treatment	8 (8–20)	10 (6–12)	12 (6–20)	10 (6–10)
Overall response				
Clinical	22/25 (88)	13/14 (92.9)	25/35 (71.4)	20/22 (90.9)
Hormonal	18/39 (46.2)	13/22 (59.1)	12/26 (46.2)	12/16 (75)
Radiological	23/30 (76.7)	16/27 (59.3)	17/25 (68)	12/20 (60)
Clinical response				
Headache	22/25 (88)	12/13 (92.3)	25/29 (86.2)	20/20 (100)
Visual field deficits	-	-	12/22 (54.5)	11/12 (91.7)[#]
Cranial nerve palsy	-	-	3/6 (50)	7/8 (87.5)
Hormonal response				
Corticotroph	5/17 (29.4)	8/16 (50)	4/15 (26.7)	8/12 (66.7)[#]
Thyrotroph	7/20 (35)	5/12 (41.7)	7/16 (43.8)	5/10 (50)
Gonadotroph	7/21 (66.7)	7/16 (43.8)	9/16 (56.3)	5/10 (50)
Somatotroph	3/7 (42.9)	0/9 (0)	5/8 (62.5)	2/4 (50)
Prolactin normalization	8/12 (66.7)	8/10 (80)	6/7 (85.7)	5/6 (83.3)
Diabetes insipidus recovery	3/16 (18.8)	7/17 (41.2)	6/11 (54.5)	1/5 (20)
Radiological response				
Regression in pituitary mass	15/22 (68.2)	16/20 (80)	21/24 (87.5)	16/20 (80)
Resolution of stalk thickening	19/22 (86.4)	16/25 (64)	12/19 (63.2)	10/16 (62.5)
Need for rescue therapy	17/44 (38.6)	4/31 (12.9)[*]	13/35 (37.1)	6/23 (26.1)

Data are expressed as *n*/N (%) or median (interquartile range).
[*]$P < 0.05$ between oral and i.v. glucocorticoids in mild-moderate cases; [#]$P < 0.05$ between oral and i.v. glucocorticoids in severe cases.

duration of glucocorticoid therapy. The absence of diabetes insipidus and female gender predicted a better anterior pituitary hormonal recovery in the i.v. group.

PAH is characterized by inflammation of the pituitary gland leading to mass effects or pituitary hormonal deficits. Among the therapeutic options, clinical observation and glucocorticoids are both successful as first-line therapies, with surgery being reserved for a small fraction of patients. Observation may be chosen for patients who have milder disease such as headache, without evidence of visual field deficits or cranial nerve palsies, and absence of panhypopituitarism. Besides, the indication for therapeutic glucocorticoid administration, if needed, remains to be established. In the recent meta-analysis, high-dose glucocorticoids are associated with improved recovery of deficits, but optimal dosing, route, and duration are unclear (4). In the current IPD-MA, better visual field-deficit recovery, overall hormonal response (66.7% vs 45.5%), in particular corticotroph axis recovery, and a lesser need for rescue therapy were observed with an i.v. route in comparison to the oral route. Among smaller retrospective and prospective single-center studies which could not be included due to lack of individual patient data, the APH response rate tended to be better with the i.v. route (50–100% vs 17–70%) than oral route (7, 8, 9, 10, 11, 12, 13). This higher efficacy of IVSG is akin to those in neuroinflammatory conditions like optic neuritis, and multiple sclerosis, where hastened recovery and fewer relapses are observed as compared to oral glucocorticoids (14, 15). The reason for better response with the i.v. route cannot be attributed to bioavailability as glucocorticoids being lipid-soluble have similar bioavailability (70–80%) and area under the curve for equivalent doses of glucocorticoids administered through oral and i.v. routes (16, 17). However, the potency and efficacy of glucocorticoids in neuroinflammatory conditions also depend on the time to achieve peak plasma concentration and CSF concentration of glucocorticoids, which may be greater with the i.v. route (18). Another possible explanation for improved efficacy could be a higher dose administered by i.v. route as compared to oral as usually bolus doses are incorporated in the former regimens.

For analysis of the effect of dose on outcomes, we classified glucocorticoid doses into prednisolone equivalents as per the nomenclature proposed by the EULAR committee (5). We observed that overall clinical response especially visual field recovery was better with high and very high-dose vs medium-dose glucocorticoids.

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A pathophysiological explanation for improved clinical response to very high doses (>100 mg/day) is probably related to the non-specific non-genomic actions, where higher supra-physiological doses (>100 mg/day) have anti-inflammatory effects, whereas lower supra-physiological doses (<30 mg/day) are just immunomodulatory (5, 19). It has been demonstrated that the non-genomic action of glucocorticoids has a log-linear relationship with dose after ≥30 mg/day, below which it is negligible (5). An experimental study with methylprednisolone pulse therapy in autoimmune encephalitis showed higher T cell apoptosis with 10 and 50 mg/kg of i.v. methylprednisolone as compared to 1 mg/kg, thus maintaining a balance between pro- and anti-inflammatory T cell functions (18).

Additionally, corticotroph axis recovery and the need for rescue therapy were significantly better with very high-dose glucocorticoids. Early involvement of ACTH-secreting cells in PAH and subsequent hypocortisolism has been proposed to be an underlying mechanism of perpetuating the autoimmune destruction of multiple tropic hormones (20). Hence, corticotroph axis recovery by higher doses (>100 mg/day) of glucocorticoids given intravenously may have a role in preventing damage to adjacent pituitary cell types and lead to better APH recovery. Further, none of the patients included in the current study had new-onset adrenal insufficiency after glucocorticoid treatment. In the setting of pituitary disease, new-onset adrenal insufficiency could occur due to the progression of the underlying inflammatory pathology *per se* or could be due to suppression of the HPA axis by supraphysiological dose of exogenous glucocorticoids. It is difficult to differentiate between the two; however, radiological evaluation with MRI may provide insight into structural pituitary disease (either progressive enlargement or empty sella).

In our study, the beneficial effects of the i.v. route and very high-dose glucocorticoids on visual field and corticotroph axis recovery were maintained in the severe group, whereas it was not significant in the mild to moderate disease as compared to the oral route. Comparison of glucocorticoid treatment outcomes according to dose and duration in mild-moderate and severe was limited by a lesser number of cases. Thus, the glucocorticoid regimen may be tailored according to the severity of the disease with oral glucocorticoids (with medium to high dose) being considered for mild-moderate disease, whereas severe disease be treated with the i.v. route (and very high dose) (Fig. 2). Nonetheless, the APH recovery rate of 45% with oral glucocorticoids in milder cases seen in our study is better than that achieved by observation alone (21%) in the meta-analysis cohort by Donegan *et al.* (4). The decision of observation vs glucocorticoid treatment in mild-moderate cases of hypophysitis is still debatable. Since we did not include patients who underwent observation for the current review and IPD-MA, it is difficult to draw conclusion on the same. Further studies comparing observation vs glucocorticoid treatment based on disease severity are needed to address the question.

Glucocorticoid treatment duration in published literature varies with i.v. bolus dose ranging from 3 to 14 days and cumulative duration ranging from 1 to 144 weeks. We divided the duration of glucocorticoids reported in the literature into tertiles to determine the optimum duration. We found that beneficial effects on hormonal axis recovery were better in patients who received >6.5 weeks of glucocorticoids; however, neuro-ophthalmological manifestations improved even in patients with a lesser duration of treatment. The underlying mechanism of better hormonal recovery is unclear.

Recently published meta-analyses indicate that disease progression was highest (26.5%) with high-dose glucocorticoids compared to observation and surgery, irrespective of route and dose of glucocorticoid treatment administered. In the present study, we observed a lesser (18% vs 37.5%) need for rescue therapy with the i.v. route and very high dose (17.3% vs 53.3%) compared to medium dose. Thus, administration of a very high dose of glucocorticoids by i.v. route may help prevent the occurrence of disease progression or recurrences.

The concerns in administering longer duration and higher doses of glucocorticoids are related to the side effects on bone health and metabolism. In the current analysis, weight gain and cushingoid features were seen in 10% each and psychiatric symptoms in 5% of patients receiving

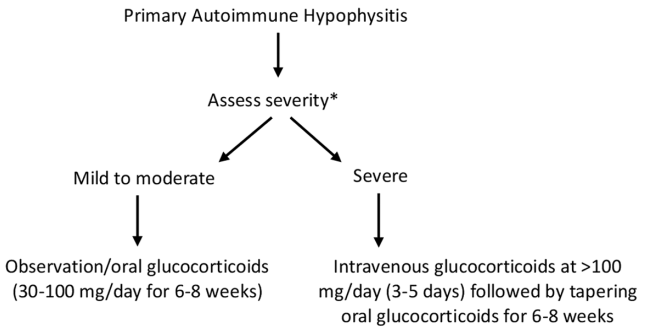

Figure 2
Suggested management algorithm for patients diagnosed with primary autoimmune hypophysitis. *Severe disease: presence of either of the following: visual field deficit, cranial nerve palsy, severe headache, worsening neuro-opthalmologic symptoms/signs. Mild to moderate: absence of severe features.

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glucocorticoids. In a series by Wang *et al.*, cushingoid features occurred in 59.3% of patients on glucocorticoids, which disappeared during reduction or withdrawal. The relatively lower prevalence of adverse events in the current analysis could be due to reporting bias or non-capturing of transient hyperglycemia, weight gain with or without cushingoid features, and psychiatric effects which subside after stopping the treatment. Nonetheless, in patients with progressive or recurrent disease needing long-term glucocorticoids, alternative glucocorticoid-sparing immunosuppressive therapies could be considered (1).

There were no significant predictors of response to oral glucocorticoids. In IVSG, the prevalence of DI was higher in patients who did not have APH recovery. The evidence for DI as a prognostic factor in endocrine function recovery has contradictory findings. A retrospective study from an infundibulo-neurohypophysitis predominant cohort from Italy showed DI as an adverse prognostic factor, which may be due to irreversible damage caused by infiltration of the pituitary stalk, whereas another Italian study showed thickened pituitary stalk and DI as favorable factors for APH recovery (8, 21). Other factors such as the radiological subtype of PAH might play a role in recovery since the vascular anatomy of the stalk is different from the anterior pituitary (22). Further, the duration of symptoms was numerically longer in patients who did not respond as compared to responders in both OSG and IVSG. The efficacy of glucocorticoids diminishes during the later stages of PAH once irreversible fibrosis sets in.

The limitations of the study include reporting bias in published literature, limited availability of hormonal outcomes, and adverse effects in all cases. The review predominantly includes case reports with very few prospective/retrospective studies forming a weak level of evidence. Further, there was a lack of clear subtyping of PAH into anterior, pan, or infundibulo-neurohypophysitis, which may have influenced the results. Due to the nature of the study or data collection, it would have been possible that milder severity patients were observed and the severe/progressive patients would have been offered therapeutic glucocorticoid administration. Since we did not include patients who underwent observation for the current review and IPD-MA, it is difficult to draw a conclusion on the same. Further studies comparing observation vs glucocorticoid treatment in milder disease are needed to address the question. Nonetheless, to the best of our knowledge, this is the first IPD-MA of PAH and the outcomes of this study may help in choosing the optimal route, dose, and duration of glucocorticoids, especially for severe cases of primary hypophysitis.

Conclusion

In this systematic review and IPD-MA on the use of glucocorticoids in PAH, we observed a better improvement in the visual field and corticotroph axis recovery with the i.v. route, very high dose, and cumulative longer duration (>6.5 weeks) of glucocorticoids, especially in severe disease. The study also suggests that high-dose oral glucocorticoid treatment may be of use for mild to moderate cases of PAH. Larger prospective studies of glucocorticoid administration across varying severity and radiological subtypes with a uniform hormonal evaluation with complete data on adverse events are required.

Supplementary materials
This is linked to the online version of the paper at https://doi.org/10.1530/EC-22-0311.

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Human participants and/or animal rights statement
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