Low Incidence of Corticosteroid-Associated Adverse Events with Long-term Exposure to Low-dose Prednisone Given with Abiraterone Acetate to Metastatic Castration-resistant Prostate Cancer Patients

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ABSTRACT

Background: Abiraterone acetate (hereafter abiraterone) is the prodrug of abiraterone, which inhibits CYP17A1 and testosterone synthesis and prolongs survival of patients with metastatic castration-resistant prostate cancer (mCRPC). Abiraterone plus prednisone is approved for the treatment of patients with mCRPC.

Objective: To investigate whether long-term use of low-dose prednisone with/without abiraterone leads to corticosteroid-associated adverse events (AEs) in mCRPC patients.

Design, Setting, and Participants: 2267 patients in COU-AA-301 and COU-AA-302 were included. We used an inclusive Standardized MedDRA Queries–oriented approach to identify 112 preferred terms for known corticosteroid-associated AEs, and assessed the incidence of corticosteroid-associated AEs during 3-month exposure intervals and across all prednisone exposure.

Intervention: All 2267 patients received 5 mg prednisone twice daily. 1333/2267 received abiraterone (1 g) plus prednisone.

Results and Limitations: The incidence of corticosteroid-associated AEs for any-grade and grade ≥3 corticosteroid-associated AEs with any prednisone exposure was 25%, 26%, and 23% and 5%, 5%, and 4% for all patients, abiraterone plus prednisone, and prednisone alone, respectively. The most common any-grade corticosteroid-associated AEs were hyperglycemia (7.4%, 7.8%, and 6.9% for all patients, abiraterone plus prednisone, and prednisone alone, respectively) and weight increase (4.3%, 3.9%, and 4.8%, respectively). When assessed by duration of exposure (3-month intervals up to ≥30 months), no discernable trend was observed in corticosteroid-associated AEs, including hyperglycemia and weight increase. The investigator-

reported study discontinuation rate due to corticosteroid-associated AEs was 11/2267 (0.5%), and one patient had a corticosteroid-associated AE resulting in death.

Conclusions: Low-dose prednisone given with or without abiraterone is associated with an overall low incidence of corticosteroid-associated AEs. The frequency of corticosteroid-associated AEs remained low with increased duration of exposure to prednisone.

Patient Summary: We assessed AEs in mCRPC patients treated long-term with a low dose of a corticosteroid. We found that long-term treatment with this low-dose corticosteroid is safe and tolerable.

1. Introduction

Abiraterone acetate (hereafter abiraterone) is the prodrug of abiraterone, which selectively blocks cytochrome P450 C17 (CYP17). CYP17 is required for androgen biosynthesis, which occurs in testicular, adrenal, and prostatic tumor tissue [1-3]. Abiraterone plus prednisone is approved for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) based on a demonstrated survival benefit and a favorable tolerability profile in both the pre- and postchemotherapy settings [4-8]. In the final analysis of the phase 3 COU-AA-301 trial of postchemotherapy patients with mCRPC, abiraterone plus prednisone significantly prolonged median overall survival (OS) by 4.6 months (26% risk reduction of death vs placebo plus prednisone [hereafter prednisone alone]).[4,5] Compared with prednisone alone, abiraterone plus prednisone significantly prolonged OS by 4.4 months (19% risk reduction of death vs prednisone alone) in the final analysis of the phase 3 COU-AA-302 trial of prechemotherapy patients with mCRPC [6-8].

Corticosteroids may be used by patients with cancer, including those with mCRPC, to manage cancer-related pain and weight loss, and the side-effects of chemotherapy [9,10]. Long-term use of moderate-/high-dose corticosteroids (eg, ≥20 mg/d prednisone) has an established adverse event (AE) profile [11,12]. A list of common corticosteroid-associated AEs can be found in the Methods section. There are some concerns about whether similar frequency and severity of side-effects would be seen with long-term coadministration of low-dose prednisone with abiraterone. To address this question, we used the COU-AA-301 and COU-AA-302 data sets to investigate whether long-term use of low-dose prednisone with or without abiraterone in patients with mCRPC leads to corticosteroid-associated AEs.

2. Patients and methods

The design, eligibility criteria, and efficacy results for COU-AA-301 (NCT00638690) and COU-AA-302 (NCT00887198) have been described previously [4-8]. Briefly, COU-AA-301 and COU-AA-302 were phase 3 trials of patients randomized 2:1 and 1:1, respectively, to abiraterone (1 g) plus prednisone or prednisolone (5 mg BID) (hereafter prednisone) or prednisone alone in the post-docetaxel and chemotherapy-naïve mCRPC settings, respectively [4-8]. A total of 1195 patients were enrolled in COU-AA-301 (abiraterone plus prednisone, $n = 797$; prednisone alone, $n = 398$).[4,5] A total of 1088 patients were enrolled in COU-AA-302 (abiraterone plus prednisone, $n = 546$; prednisone alone, $n = 542$) [6-8]. A combined total of 2267 patients in COU-AA-301 and COU-AA-302 were included in the safety population and received 5 mg BID prednisone. Of these, 1333 patients received abiraterone plus prednisone.

We used an inclusive Standardized MedDRA Queries–oriented approach to identify 116 preferred terms for known corticosteroid-associated AEs based on the prednisone label to interrogate the COU-AA-301 and COU-AA-302 databases. Irrelevant preferred terms were excluded, and upcoding strategies were employed to convert and match with legacy MedDRA versions (version 17 used for these analyses). Corticosteroid-associated AEs of interest were as follows:

- **Endocrine disorders:** adrenal insufficiency, Cushing's syndrome, Cushingoid state, pituitary-dependent Cushing's syndrome
- **Eye disorders:** cataract, cataract cortical, cataract subcapsular

- **Gastrointestinal disorders:** chronic gastrointestinal bleeding, duodenal perforation, duodenal ulcer, duodenal ulcer hemorrhage, duodenal ulcer perforation, duodenal ulcer perforation (obstructive), duodenal ulcer (obstructive), duodenitis (hemorrhagic), erosive duodenitis, erosive esophagitis, feces discolored, gastric hemorrhage, gastric perforation, gastric ulcer, gastric ulcer hemorrhage, gastric ulcer hemorrhage (obstructive), gastric ulcer perforation, gastric ulcer perforation (obstructive), gastritis (erosive), gastritis (hemorrhagic), gastroduodenal hemorrhage, gastroduodenal ulcer, gastroduodenitis (hemorrhagic), gastrointestinal erosion, gastrointestinal hemorrhage, gastrointestinal perforation, gastrointestinal ulcer, gastrointestinal ulcer hemorrhage, gastrointestinal ulcer perforation, hematemesis, hematochezia, hemorrhagic erosive gastritis, jejunal ulcer, jejunal ulcer perforation, melena, esophageal hemorrhage, esophageal perforation, esophageal ulcer, esophageal ulcer hemorrhage, esophageal ulcer perforation, esophageal varices hemorrhage, esophagitis (hemorrhagic), esophagitis (ulcerative), peptic ulcer, peptic ulcer hemorrhage, peptic ulcer perforation, peptic ulcer perforation (obstructive), peptic ulcer (obstructive), proctitis (hemorrhagic), upper gastrointestinal hemorrhage
- **General disorders and administration site conditions:** impaired healing, perforated ulcer
- **Infections and infestations:** peptic ulcer helicobacter
- **Injury, poisoning, and procedural complications:** acetabulum fracture, atypical femur fracture, cervical vertebral fracture, femoral neck fracture, forearm fracture, hip fracture, lumbar vertebral fracture, rib fracture, spinal compression fracture, thoracic vertebral fracture, wrist fracture

- **Investigations:** blood glucose abnormal, blood glucose fluctuation, blood glucose increased, body mass index increased, bone density decreased, gastric occult blood positive, glucose tolerance decreased, glucose tolerance test abnormal, glucose urine present, glycosylated hemoglobin increased, occult blood positive, weight increase
- **Metabolism and nutrition disorders:** abnormal weight gain, central obesity, diabetes mellitus, diabetes mellitus inadequate control, glucose tolerance impaired, hyperglycemia, impaired fasting glucose, insulin-requiring type 2 diabetes mellitus, metabolic syndrome
- **Musculoskeletal and connective tissue disorders:** bone formation decreased, bone loss, myopathy, myopathy toxic, osteopenia, osteoporosis, osteoporotic fracture, resorption bone increased, spinal deformity
- **Renal and urinary disorders:** glycosuria
- **Skin and subcutaneous disorders:** ecchymosis, hemorrhage (subcutaneous), hemorrhage (subepidermal), purpura, skin atrophy, skin fragility, skin hemorrhage, skin striae
- **Surgical and medical procedures:** cataract operation, duodenal ulcer repair, gastrointestinal ulcer management, perforated peptic ulcer oversewing

The incidence of corticosteroid-associated AEs during 3-month exposure intervals and across the entire exposure to prednisone was assessed as number of patients with an AE divided by number of patients at risk. Data are represented as all patients (any prednisone), abiraterone plus prednisone, and prednisone alone.

3. Results

Patient demographics were similar in COU-AA-301 and COU-AA-302. Patients enrolled in COU-AA-302 were asymptomatic/mildly symptomatic and had no visceral metastases, and therefore had a lower disease burden than patients in COU-AA-301, who had more advanced disease (Table 1).

A total of 2267 patients in COU-AA-301 and COU-AA-302 received prednisone 5 mg BID for a median of 8.3 months (range, 0.1–34.9 months), which represents 2006 patient-years of exposure, defined as the sum of the number of years that each patient in a study population has been treated with prednisone.

3.1. Safety

The safety populations in COU-AA-301 and COU-AA-302 included all randomized patients who received any study medication ($N = 2267$). The overall incidence of corticosteroid-associated AEs observed in patients in COU-AA-301 and COU-AA-302 is shown in Table 2.

The overall incidence of any-grade corticosteroid-associated AEs for any prednisone exposure was 24.6%, 25.5%, and 23.3% for all patients, abiraterone plus prednisone, and prednisone alone, respectively (Fig. 1A). The two most common any-grade corticosteroid-associated AEs were hyperglycemia (7.4%, 7.8%, and 6.9% for all patients, abiraterone plus prednisone, and prednisone alone, respectively) and weight increase (4.3%, 3.9%, and 4.8%, respectively). Other

any-grade AEs occurring in ≥1% of patients were ecchymosis, rib fracture, Cushingoid state, cataract, diabetes mellitus, and skin atrophy (Table 2).

The incidence of grade ≥3 corticosteroid-associated AEs for any prednisone exposure was 4.5%, 5.1%, and 3.7% for all patients, abiraterone plus prednisone, and prednisone alone, respectively (Fig. 1B). The two most common grade ≥3 corticosteroid-associated AEs were hyperglycemia and cataract. Other grade ≥3 AEs occurring in ≥0.1% of patients are listed in Table 2.

When assessed by duration of exposure in 3-month intervals for a median of 8.3 months (range, 0.1–34.9 months), any-grade corticosteroid-associated AEs fluctuated between 0% and 12%, but no discernable trend was observed (Fig. 2A). Grade ≥3 corticosteroid-associated AEs fluctuated between 1% and 2% when assessed by duration of exposure (Fig. 2B). We assessed the incidence of any-grade hyperglycemia and any-grade weight increase, the two most common corticosteroid-associated AEs, by duration of exposure in 3-month intervals up to ≥30 months. No discernible trend was observed in overall hyperglycemia (Fig. 3) and weight increase (Fig. 4).

Only grade 1 and grade 2 weight increase were observed in this combined patient population, and most cases (76 of 97; 78%) were grade 1. There were no incidences of grade ≥3 weight increase. Grade 1 weight increase was defined as a 5 to <10% increase from baseline, and grade 2 weight increase was defined as a 10 to <20% increase from baseline, according to the Common Terminology Criteria for Adverse Events (version 4.0). As weight gain is a common concern for patients receiving corticosteroids, we evaluated change in weight over time, which shows that

abiraterone plus prednisone had a minimal impact (Fig. 5). Furthermore, of the 33 patients with Cushingoid state (all grade 1 or 2), which frequently presents with central adiposity among other phenotypic characteristics, only four had increased weight.

The investigator-reported study discontinuation rate due to corticosteroid-associated AEs was 0.6% (8/1333) for abiraterone plus prednisone and 0.3% (3/934) for prednisone alone. The discontinuations in the abiraterone plus prednisone group were attributed to hip fracture (1), spinal fracture (2), spinal compression fracture (1), gastrointestinal hemorrhage (2), melena (1), and adrenal insufficiency (1). In the prednisone alone group, skin hemorrhage (1), diabetes mellitus (1), and upper gastrointestinal hemorrhage (1) were cited by the investigator as reasons for discontinuation. One patient in COU-AA-301 had a corticosteroid-associated AE that resulted in death; sponsor assessment of the cause of death was upper gastrointestinal hemorrhage.

4. Discussion

This analysis, which specifically assessed known corticosteroid-associated AEs based on the prednisone label, demonstrates that low-dose prednisone (5 mg BID) given with or without abiraterone to men with mCRPC is associated with an overall low incidence of corticosteroid-associated AEs. The frequency of corticosteroid-associated AEs remained low, even with increased duration of exposure to low-dose prednisone. Furthermore, the low rate of discontinuation due to corticosteroid-associated AEs confirms the manageability of these AEs in the few cases where they do arise. Addition of abiraterone to prednisone did not appear to increase the incidence of corticosteroid-associated AEs, addressing concerns about the long-term

coadministration of this combination.

There are a few limitations to our study. First, the lack of a placebo-only comparator arm makes it impossible to assess the baseline frequency of these AEs in this population without steroid exposure. This limitation further precludes us from determining whether grade ≥ 3 AEs in high-risk patients arise from an underlying condition or from low-dose prednisone use. Nevertheless, the absence of an increase in corticosteroid-associated AE frequency over time, after ≥30 months of exposure to prednisone, provides strong evidence in support of our conclusions. Second, there were low numbers of evaluable patients at later time points, with <50% of patients remaining by 12 months and ~10% remaining by 24 months. Finally, this was a retrospective analysis, and therefore patient physiological status, comorbidities, and other baseline factors that may impact the interpretation of these findings were not prespecified. The ongoing phase 3 Latitude trial (NCT01715285) is evaluating the coadministration of abiraterone plus androgen deprivation therapy plus 5 mg prednisone in patients with hormone-naïve de novo metastatic prostate cancer, which will allow for the prospective assessment of daily low-dose prednisone.

5. Conclusions

Taken together, the results reported herein support those of previous studies that demonstrated that that long-term treatment with abiraterone plus low-dose prednisone is well tolerated. These results further show that the incidence of corticosteroid-associated AEs in patients with mCRPC after long-term administration of low-dose prednisone is low and manageable.

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Figure legends

Fig. 1 – Overall incidence of corticosteroid-associated any-grade (A) and grade ≥3 (B) adverse events. AA = abiraterone acetate; P = prednisone.

Fig. 2 - Incidence of new onset corticosteroid-associated any-grade (A) and grade ≥ 3 (B) adverse events by exposure. AA = abiraterone acetate; P = prednisone.

Fig. 3 – Incidence of any-grade hyperglycemia by exposure. AA = abiraterone acetate; P = prednisone.

Fig. 4 – Incidence of grade 1 and grade 2 weight increase by exposure. AA = abiraterone acetate; P = prednisone.

Fig. 5 – Weight change from baseline in COU-AA-301 and COU-AA-302 by exposure. AA = abiraterone acetate; P = prednisone.

293 **Table 1 – Baseline characteristics of patients in COU-AA-301 and COU-AA-302**

Baseline characteristics	COU-AA-301 *N* = 1195	COU-AA-302 *N* = 1088
Age, years		
Median (range)	69 (39–95)	70 (44–95)
Gleason score at initial diagnosis, n (%)	***n* = 1047**	***n* = 996**
≤7	502 (48)	479 (48)
≥8	545 (52)	517 (52)
Extent of disease, n (%)	***n* = 1190**	***n* = 1086**
Bone	1066 (90)	884 (81)
Bone only	474 (40)	541 (50)
Soft tissue or node	709 (60)	538 (50)
Other	60 (5)	11 (1)
Time from initial diagnosis to first dose, years		
Median (range)	6.02 (0.17–25.01)	5.3 (0–28)
Weight (kg)	82.6 (39.2–203.3)	
Median (range)		87.5 (45.3–168.3)
PSA (ng/ml)		
Median (range)	131.4 (0.4–10114)	39.51 (0–6606.4)
Hemoglobin (g/dl)		
Median (range)	11.8 (7.2–16.5)	13.1 (7–16.6)
LDH (IU/l)		
Median (range)	227 (84–5125)	185 (60–871)
ALP (IU/l)		
Median (range)	134 (20–4896)	91 (21–3056)

294 PSA = prostate-specific antigen; LDH = lactate dehydrogenase; ALP = alkaline phosphatase.

295 **Table 2 – All corticosteroid-associated adverse events in COU-AA-301 and COU-AA-302**

	***N* = 2267**	
	Any-grade	**Grade ≥3**
Patients with an AE, n (%)	**558 (24.6)**	**103 (4.54)**
Hyperglycemia	168 (7.4)	48 (2.0)
Weight increase	97 (4.3)	0
Ecchymosis	66 (2.9)	0
Rib fracture	53 (2.3)	2 (0.1)
Cushingoid state	33 (1.5)	0
Cataract	30 (1.3)	10 (0.4)
Diabetes mellitus	26 (1.1)	8 (0.4)
Skin atrophy	23 (1.0)	0
Hematochezia	20 (0.9)	2 (0.1)
Purpura	19 (0.8)	1 (<0.1)
Osteoporosis	20 (0.9)	2 (0.1)
Myopathy	18 (0.8)	2 (0.1)
Spinal compression fracture	14 (0.6)	3 (0.1)
Gastrointestinal hemorrhage	10 (0.4)	7 (0.3)
Osteopenia	10 (0.4)	0
Melena	9 (0.4)	3 (0.1)
Adrenal insufficiency	8 (0.4)	3 (0.1)
Wrist fracture	8 (0.4)	1 (< 0.1)

Hip fracture	5 (0.2)	3 (0.1)
Cataract operation	4 (0.2)	2 (0.1)
Hematemesis	4 (0.2)	1 (<0.1)
Lumbar vertebral fracture	4 (0.2)	1 (<0.1)
Spinal fracture	4 (0.2)	2 (0.1)
Diabetes mellitus (inadequate control)	4 (0.2)	0
Skin fragility	4 (0.2)	0
Feces discolored	4 (0.2)	0
Cervical vertebral fracture	3 (0.1)	2 (0.1)
Gastric ulcer	3 (0.1)	1 (<0.1)
Osteoporotic fracture	3 (0.1)	1 (<0.1)
Thoracic vertebral fracture	3 (0.1)	0
Impaired healing	3 (0.1)	0
Upper gastrointestinal hemorrhage	2 (0.1)	2 (0.1)
Glucose tolerance impaired	2 (0.1)	1 (<0.1)
Skin hemorrhage	2 (0.1)	0
Cushing's syndrome	2 (0.1)	0
Femoral neck fracture	1 (<0.1)	1 (<0.1)
Central obesity	1 (<0.1)	0
Hemorrhage subcutaneous	1 (<0.1)	0
Skin striae	1 (<0.1)	0
Blood glucose fluctuation	1 (<0.1)	0
Occult blood positive	1 (<0.1)	0

Duodenal ulcer	1 (<0.1)	0
Gastric hemorrhage	1 (<0.1)	0
Gastritis erosive	1 (<0.1)	0
Gastritis hemorrhagic	1 (<0.1)	0
Peptic ulcer	1 (<0.1)	0
Bone loss	1 (<0.1)	0
Pituitary-dependent Cushing's syndrome	1 (<0.1)	0
Glycosuria	1 (<0.1)	0

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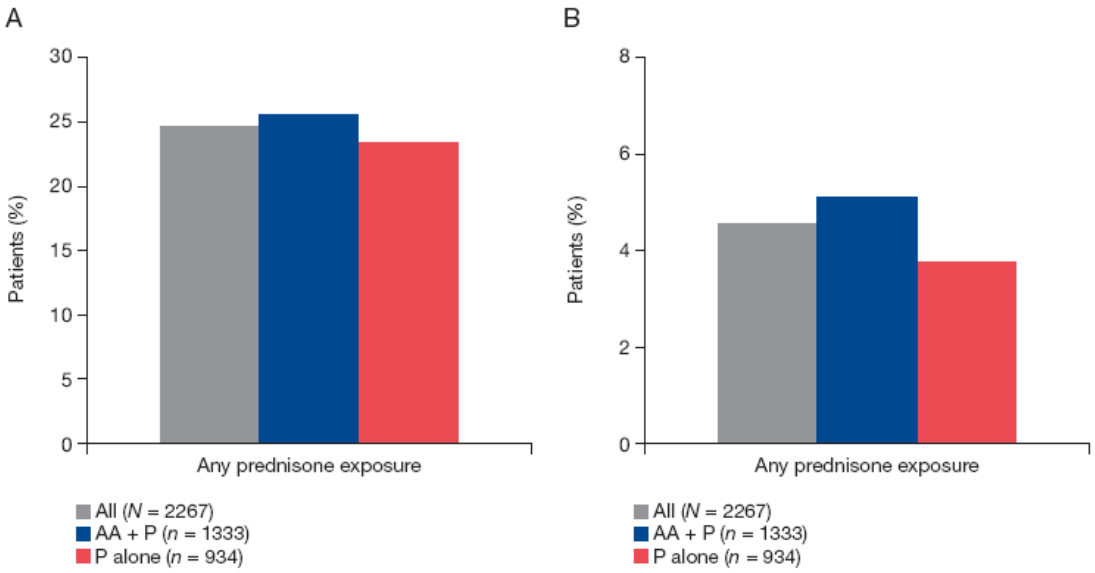
297 **Fig. 1**



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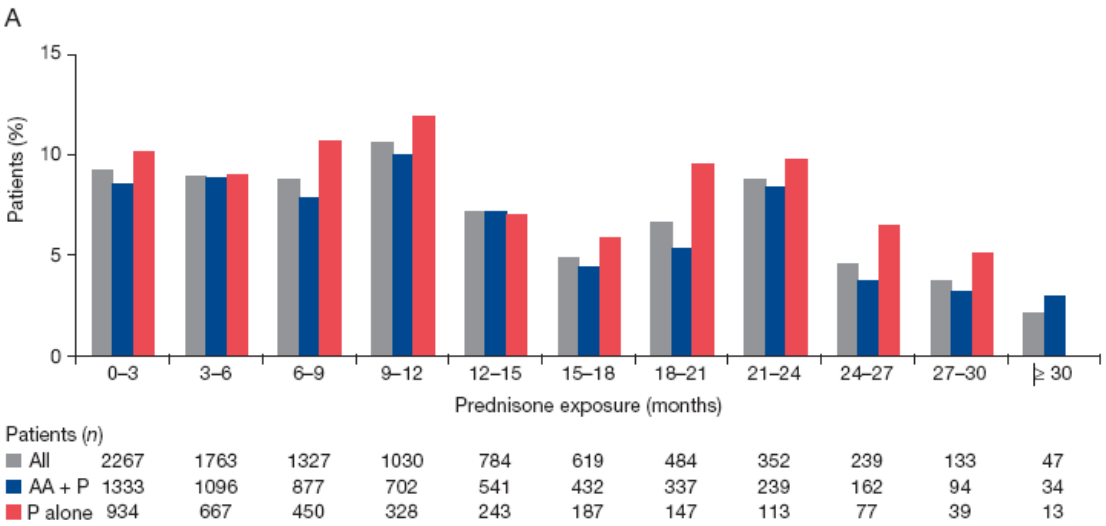
300 **Fig. 2**



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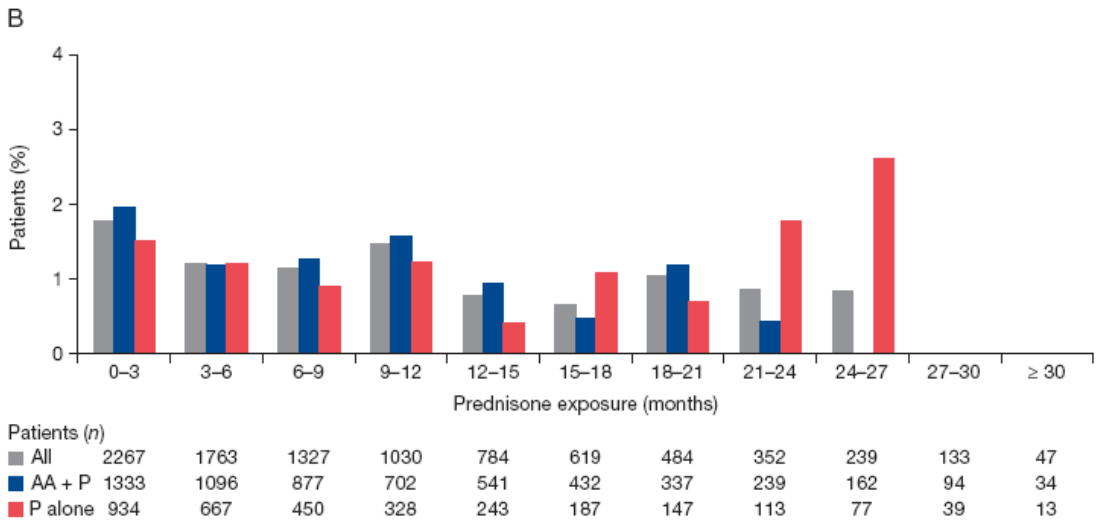

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304 **Fig. 3**

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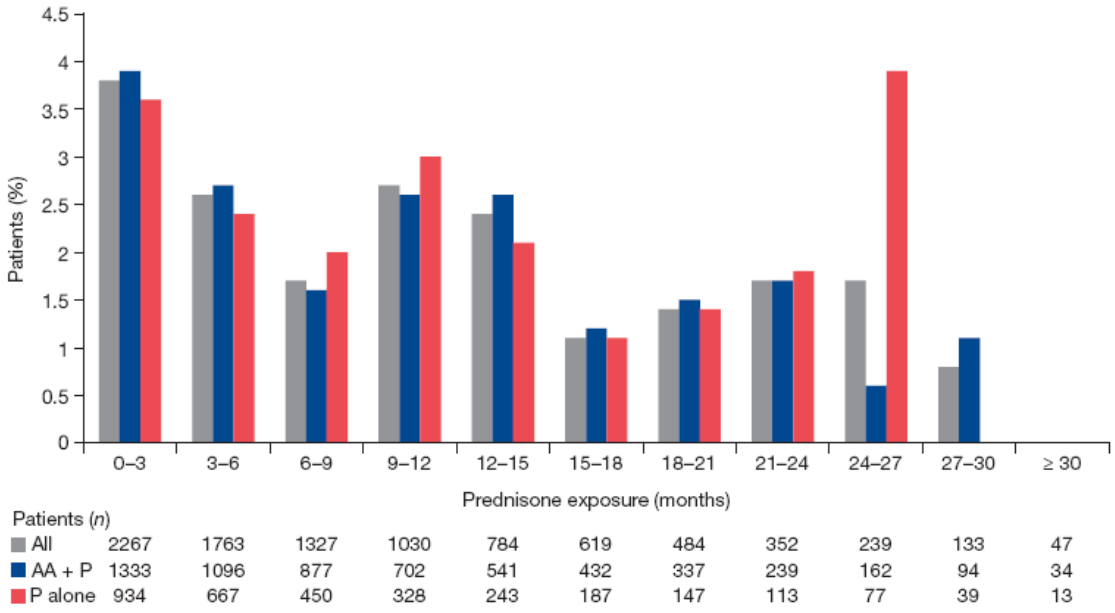

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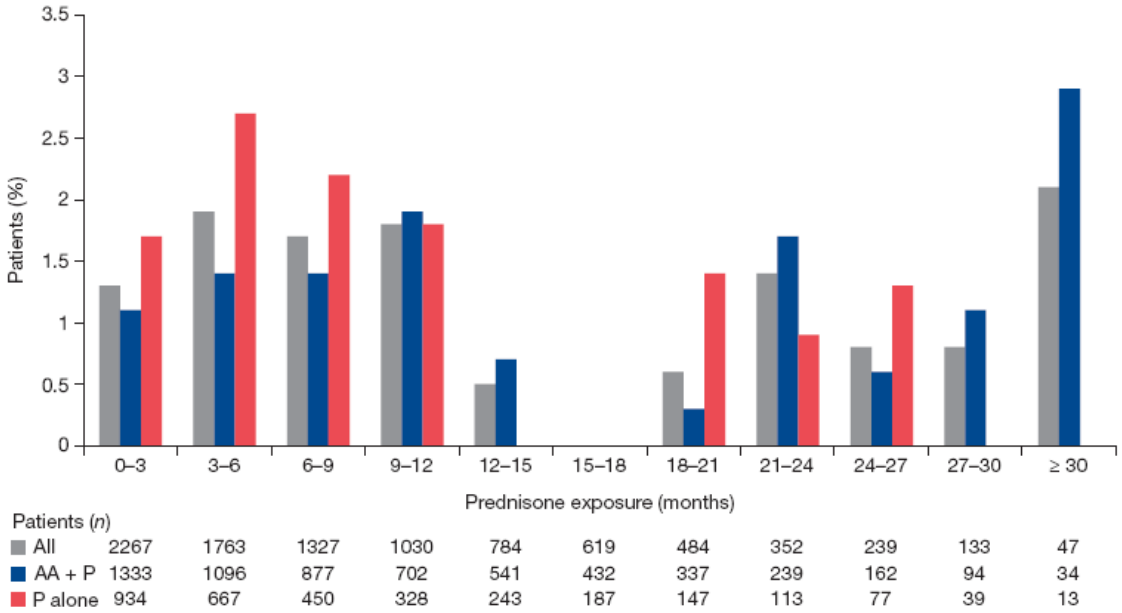

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314 **Fig. 5**

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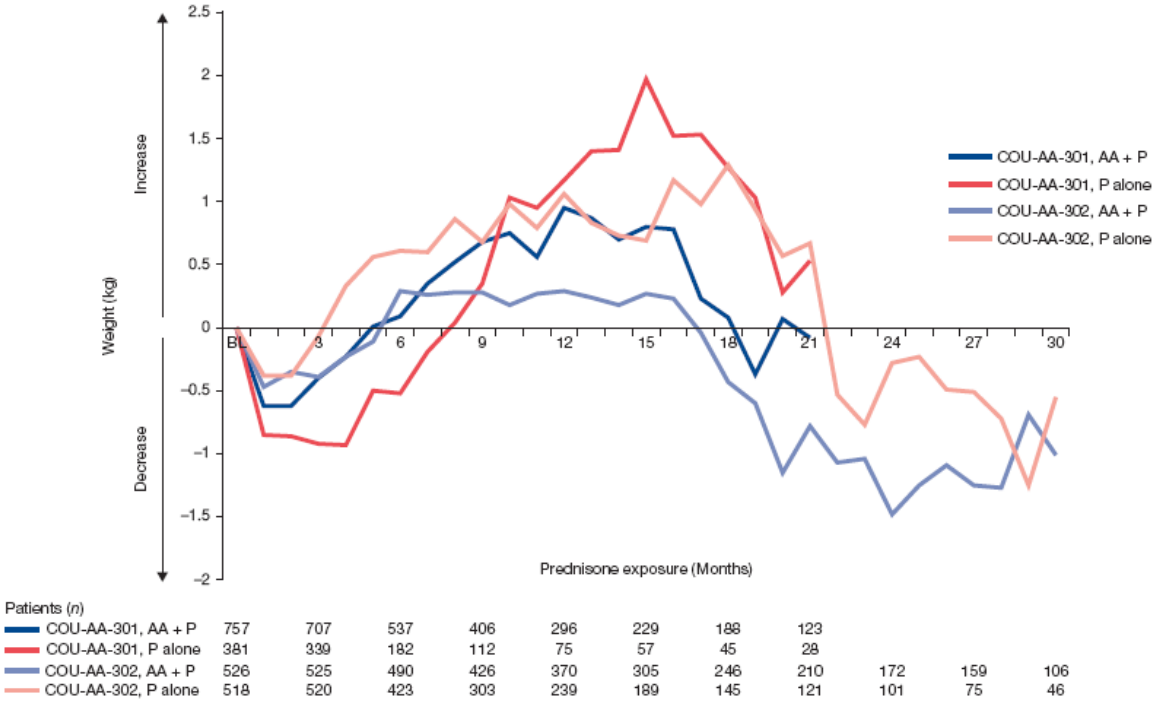

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