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Clinical Research Article

The Changing Face of Drug-induced Adrenal Insufficiency in the Food and Drug Administration Adverse Event Reporting System

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Abstract

Context: Adrenal insufficiency (AI) is a life-threatening condition complicating heterogeneous disorders across various disciplines, with challenging diagnosis and a notable drug-induced component.

Objective: This work aimed to describe the spectrum of drug-induced AI through adverse drug event reports received by the US Food and Drug Administration (FDA).

Methods: A retrospective disproportionality analysis reporting trends of drug-induced AI was conducted on the FDA Adverse Event Reporting System (FAERS) (> 15 000 000 reports since 2004). AE reports were extracted from FAERS over the past 2 decades. Interventions included cases containing any of the preferred terms in the Medical Dictionary for Regulatory Activities describing AI, and signals of disproportionate reporting for drugs recorded in 10 or more cases as primary suspect.

Results: We identified 8496 cases of AI: 97.5% serious, 41.1% requiring hospitalization. AI showed an exponential increase throughout the years, with 5282 (62.2%) cases in 2015 to 2020. We identified 56 compounds associated with substantial disproportionality: glucocorticoids (N = 1971), monoclonal antibodies (N = 1644, of which N = 1330 were associated with immune checkpoint inhibitors—ICIs), hormone therapy (N = 291), anti-infectives (N = 252), drugs for hypercortisolism or adrenocortical cancer diagnosis/treatment (N = 169), and protein kinase inhibitors (N = 138). Cases of AI by glucocorticoids were stable in each 5-year period (22%-27%), whereas those by monoclonal antibodies, largely ICIs, peaked from 13% in 2010 to 2015 to 33% in 2015 to 2020.

Conclusion: We provide a comprehensive insight into the evolution of drug-induced AI, highlighting the heterogeneous spectrum of culprit drug classes and the emerging increased reporting of ICIs. We claim for the urgent identification of predictive factors for drug-induced AI, and the establishment of screening and educational protocols for patients and caregivers.

Key Words: adrenal insufficiency, drug-induced, iatrogenic, glucocorticoid, withdrawal, checkpoint, immune checkpoint inhibitors, cancer, FDA, FAERS

Abbreviations: ACTH, adrenocorticotropin; AE, adverse event; AI, adrenal insufficiency; FAERS, Food and Drug Administration Adverse Event Reporting System; FDA, US Food and Drug Administration; HLT, high-level term; HPA, hypothalamic-pituitary-adrenal; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; PT, preferred term; ROR, reporting odds ratio; VEGFR, vascular endothelial growth factor receptor.

Iatrogenic suppression of the hypothalamic-pituitary-adrenal (HPA) axis has been recognized as a relevant clinical issue since the mid-20th century, when widespread glucocorticoid use was identified as the main cause of drug-induced adrenal insufficiency (AI) (1). After more than half a century, drug-induced AI still represents a current concern because of the large use of glucocorticoids and novel medications used to manage chronic inflammatory and immune diseases (2). In addition, several drugs interfering with steroid synthesis and metabolism (in particular, opioids, antiretroviral agents, antifungals, and testosterone synthesis inhibitors) have been marketed, further complicating the panorama of drug-induced AI. Recently, immune checkpoint inhibitors (ICIs), approved for the treatment of an increasing number of various cancer types, have been reported in cases of AI (3).

The clinical relevance of AI is noteworthy because this is a life-threatening condition leading to adrenal crisis and eventually death, if not promptly diagnosed and treated. The recognition of drug-induced AI is a clinical challenge for virtually every physician working with patients with chronic inflammatory disorders, immune diseases, and malignant tumors, among other conditions. This holds true because the presenting symptoms of AI, mostly nausea, chronic fatigue, hypotension, and gastrointestinal discomfort, often overlap

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with those of diseases requiring the drugs potentially capable of inducing AI. Also, most drug-related adverse events (AEs) may mimic and mask the symptoms of AI.

Spontaneous reporting systems, such as the Food and Drug Administration Adverse Event Reporting System (FAERS), are a crucial source of postmarketing real-world data to map the safety profile of drugs, especially in the oncological area, complementing evidence from clinical trials and offering a real-time overview of major toxicities, thus informing clinical practice for proactive monitoring and targeted management strategies (4).

Considering the evolving complexity of the clinical consequences of the HPA axis suppression induced by drugs, we performed a pharmacovigilance study aiming at describing the spectrum of drug-induced adrenal insufficiency over the last 2 decades using the FAERS database.

Materials and Methods

Data Source and Study Design

FAERS is one of the largest publicly available repositories of unsolicited reports, gathering more than 15 million reports worldwide since 2004; it was already used to early identify and characterize AEs for recently marketed drugs as well as for continuous monitoring of safety issues for old drugs (5).

We performed a retrospective, disproportionality analysis of FAERS data (up to 2020), which were downloaded (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html) and processed to remove duplicates (ie, reports overlapping in key prespecified fields, including active substance(s), AEs, event date, age, sex, reporter country, weight) and select reports of interest (Supplementary Material 1) (6).

In the FAERS database, AEs are coded through the Medical Dictionary for Regulatory Activities (MedDRA) terminology in terms of signs/symptoms, called preferred terms (PTs). AEs of interest were identified using PTs under the high-level term (HLT) "adrenal cortical hypofunctions," which comprises the following 13 PTs: *adrenal insufficiency*, *adrenocortical insufficiency acute*, *secondary adrenocortical insufficiency*, *Addison's disease*, *adrenal suppression*, *hypoaldosteronism*, *adrenal atrophy*, *steroid withdrawal syndrome*, *primary adrenal insufficiency*, *mineralocorticoid deficiency*, *glucocorticoid deficiency*, and *immune-mediated adrenal insufficiency*. Owing to low specificity, we excluded a priori the HLTs "adrenal gland disorders" and "anterior pituitary hypofunction," as well as PTs related to electrolyte imbalances (eg, hyponatremia or hyperkalemia), *adrenalitis*, *hypotension*, and *fatigue* (a likely confounding factor in cancer patients), thereby reducing the likelihood of misclassification. In this study, exposure assessment considered drugs recorded as primary suspect.

Descriptive Analysis

Reports were first described in terms of patient demographics (sex, age, country, type of reporter) and main clinical features, including fatality proportion (ie, death reported as the outcome), and seriousness (focusing on events resulting in hospitalization). Based on the FDA received date recorded in the reports, the proportion of cases were plotted over time to show the evolving contribution of the different drugs.

Statistical Analysis

We performed the so-called disproportionality approach, a validated concept in pharmacovigilance, to assess whether suspected adrenal AEs (cases) are differentially reported with a given drug, as compared to other AEs (noncases, namely FAERS reports without AI) (7). Disproportionality was performed both at the HLT (adrenal cortical hypofunctions) and at individual PTs.

Through this so-called case/noncase approach, the reporting odds ratio (ROR) with relevant 95% CI was calculated and deemed statistically significant by common thresholds (ie, the lower limit of the 95% CI > 1) (8). The resulting statistically significant ROR identified the so-called signal of disproportionate reporting. We applied a threshold of at least 10 cases, and the Bonferroni correction to reduce the likelihood of detecting spurious associations related to multiple testing.

Analyses were performed through the open-source R software (version 4.1.1; October 8, 2021). Considering heterogeneous degrees of incompleteness, for each category we calculated percentages over reports with known values (valid percentages).

Results

Descriptive Analysis

Over the 2 decades, 10 400 290 reports were retained (Table 1). A total of 8496 cases of adrenal dysfunction were found, mostly AI (61.9%), acute adrenocortical insufficiency (10.6%), and Addison disease (7.7%). As compared to other AEs (noncases), adrenal hypofunction reports showed a higher contribution by males (44.4% vs 38.9%), from non-US geographical areas (Europe 25.2% vs 14.1%; Asia 18.6% vs 6.7%; North America 52.0% vs 75.5%), and from physicians (36.6% vs 24.7%). Younger ages (eg, children 6.7% vs 2.2%) and older patients (eg, aged 65-74 years 64.5% vs 54.4%) were both more frequently represented. A serious outcome was more often reported in adrenal hypofunction (97.5% vs 60.1%), especially hospitalization (41.1% vs 20.9%).

Adrenal hypofunction reports showed an exponential increase, with 5282 (62.2%) cases in the years 2015 to 2020. Some suspected drug classes were constantly and stably reported across the years, like glucocorticoids, which were the primary suspect in 22% to 27% reports in each 5-year period; hospitalizations and death were recorded in 513 (27%) and 69 (3.6%) cases, respectively. Monoclonal antibodies, instead, peaked from 13% in 2010 to 2015 to 33% in 2015 to 2020; hospitalizations and death were recorded in 866 (53%) and 172 (11%) cases, respectively (Fig. 1).

In the 2015 to 2020 period, the most frequently reported drugs were nivolumab (N = 612), pembrolizumab (N = 270), ipilimumab (N = 230), hydrocortisone (N = 206), triamcinolone (N = 152), and fluticasone (N = 150) (Supplementary Material 1, Fig. S1) (6); ICIs showed a steady increase (N = 433 in 2020) as compared to other monoclonal antibodies (Supplementary Material 1, Fig. S2) (6). This rise was also observed when analyzing the proportion of adrenal hypofunction reports (ie, the ratio between cases and noncases), especially for ICIs in the 2015 to 2020 period (Supplementary Material 1, Fig. S3) (6).

Glucocorticoids were also recorded as concomitant drugs in a substantial proportion of cases with other pharmacological classes, albeit with different proportions ranging from 100% (β2 agonists) to 2% (opioids). Of note, glucocorticoids were reported in 19% of cases with ICIs, as compared to 77% for other monoclonal antibodies (Supplementary Material 1, Table S1) (6). Asthenia and nausea/vomiting were more frequently

Table 1. Demographic data

	Cases of adrenal hypofunction	Noncases
Total No.		
Sex	8496 (0.08%)	10 391 794 (99.92%)
F	4314 (55.6%)	5 827 794 (61.1%)
M	3439 (44.4%)	3 715 523 (38.9%)
Missing	743 (–)	848 477 (–)
Geographic area		
North America	4175 (52.0%)	7 505 680 (75.5%)
Europe	2025 (25.2%)	1 400 031 (14.1%)
Asia	1494 (18.6%)	663 319 (6.7%)
South America	106 (1.3%)	236 081 (2.4%)
Oceania	209 (2.6%)	100 871 (1.0%)
Africa	26 (0.3%)	38 500 (0.4%)
Missing	461 (–)	447 312 (–)
Occupation		
Consumer	2136 (26.7%)	4 636 992 (47.3%)
Health care professional	462 (5.8%)	276 821 (2.8%)
Lawyer	45 (0.6%)	138 777 (1.4%)
Medical doctor	2930 (36.6%)	2 418 543 (24.7%)
Other	2085 (26.0%)	1 616 368 (16.5%)
Pharmacists	357 (4.5%)	714 563 (7.3%)
Missing	481 (–)	589 730 (–)
Age, y		
Median (25%-75%)	55 (37-67)	57 (42-69)
Age group		
Neonate	21 (0.3%)	24 421 (0.3%)
Infant	106 (1.6%)	43 132 (0.6%)
Child	437 (6.7%)	155 845 (2.2%)
Teenager	241 (3.7%)	183 154 (2.6%)
Adult, y	3748 (57.1%)	4 167 296 (59.3%)
> 65	2007 (30.6%)	2 454 010 (34.9%)
65-74	1295 (64.5%)	1 335 290 (54.4%)
75-84	604 (30.1%)	850 793 (34.7%)
≥ 85	108 (5.4%)	267 890 (10.9%)
Missing	1936 (–)	3 363 936 (–)
Outcome[a]		
Serious	8283 (97.5%)	6 245 273 (60.1%)
Death	654 (7.7%)	956 540 (9.2%)
Life-threatening	681 (8.0%)	275 150 (2.6%)
Disability	368 (4.3%)	182 641 (1.8%)
Required intervention	41 (0.5%)	48 731 (0.5%)
Hospitalization	3493 (41.1%)	2 172 595 (20.9%)
Congenital anomaly	14 (0.2%)	27 921 (0.3%)
Other serious	3032 (35.7%)	2 581 695 (24.8%)

[a]For each report the most serious outcome was selected.

coreported with monoclonal antibodies, rifampicin, and drugs for hypercortisolism; thyroid hypofunction disorders with monoclonal antibodies and protein kinase inhibitors; and dermal and epidermal disorders with glucocorticoids.

Disproportionality Analysis

The full list of 164 drugs with at least 10 cases is provided in Supplementary Material 26 (6). A signal of disproportionate reporting of adrenal cortical hypofunctions was found for 56 drugs, including monoclonal antibodies, glucocorticoids, β2 agonists, hormone therapy (eg, somatropin, levothyroxine), anti-infectives (eg, antiretrovirals, antifungal triazole derivatives, rifampicin), protein kinase inhibitors (eg, lenvatinib, cabozantinib), antithrombotics (eg, heparin), bisphosphonates (eg, alendronic acid), opioids (eg, tramadol), and drugs used for hypercortisolism or adrenocortical cancer diagnosis and/or treatment (eg, metyrapone, mitotane). Of these, 46 drugs received at least 20 reports and are shown in Fig. 2.

Among monoclonal antibodies, ICIs accounted for 5 of 9 signals of disproportionate reporting, corresponding to 1330 cases (81% of 1644 AI reports for monoclonal antibodies), including inhibitors of CTLA4 (ipilimumab), PD-1 (durvalumab), and PD-L1 (nivolumab, pembrolizumab, atezolizumab). Infliximab, tocilizumab, omalizumab, and mepolizumab emerged among nononcological monoclonal antibodies.

Peculiar signals emerged with steroid withdrawal syndrome only for glucocorticoids, including topical (mometasone, clobetasol) and intra-articular (triamcinolone) medications, with secondary adrenocortical insufficiency for ICIs, and acute adrenal crisis for hydrocortisone, fluticasone (inhaled/spray) and somatotropin.

Discussion

In the current era of big data and artificial intelligence, pharmacovigilance allows an unprecedented opportunity to inform clinical practitioners about the evolving spectrum of drug-induced diseases, thus supporting safer prescribing (9). We offer, for the first time, a comprehensive overview of more than 8000 reported cases of drug-induced AI, a general safety issue embracing different disciplines, and contribute to revisiting its changing spectrum, which is constantly evolving according to pharmacopeia.

The list of 56 drugs suspected to be associated with AI will support clinicians to increase awareness and recognition of such a life-threatening condition. The most frequently reported culprit classes were glucocorticoids and monoclonal antibodies: The former remained stable across years, whereas the latter constantly increased in the 2015 to 2020 period with the advent of immunotherapy for cancers. Signals for nononcological immune-suppressive monoclonal antibodies (eg, infliximab and omalizumab) can be influenced by the large proportion (77%) of concomitant glucocorticoids; these drugs are used for immune-mediated diseases (rheumatoid arthritis, asthma) as add-on or steroid-sparing strategy. Conversely, the plausible causative immune-mediated effect of ICIs is largely supported by clinical evidence (3); the nonnegligible proportion of cases with concomitant corticosteroids (19%) could be especially interpreted in the light of treatment of concurrent immune-related adverse events (irAEs).

Glucocorticoids are among the most widely prescribed anti-inflammatory drugs worldwide (up to 3% of the population) (10-13), dispensed on medical prescription or as over-the-counter medications, the latter mostly as topic or transdermal formulations. Iatrogenic (ie, glucocorticoid-induced) AI is a well-known potential condition occurring after glucocorticoid withdrawal and one of the most frequent causes of glucocorticoid deficiency (14). Clinically relevant AI may arise after abrupt or inappropriately managed withdrawal of glucocorticoids, especially in patients

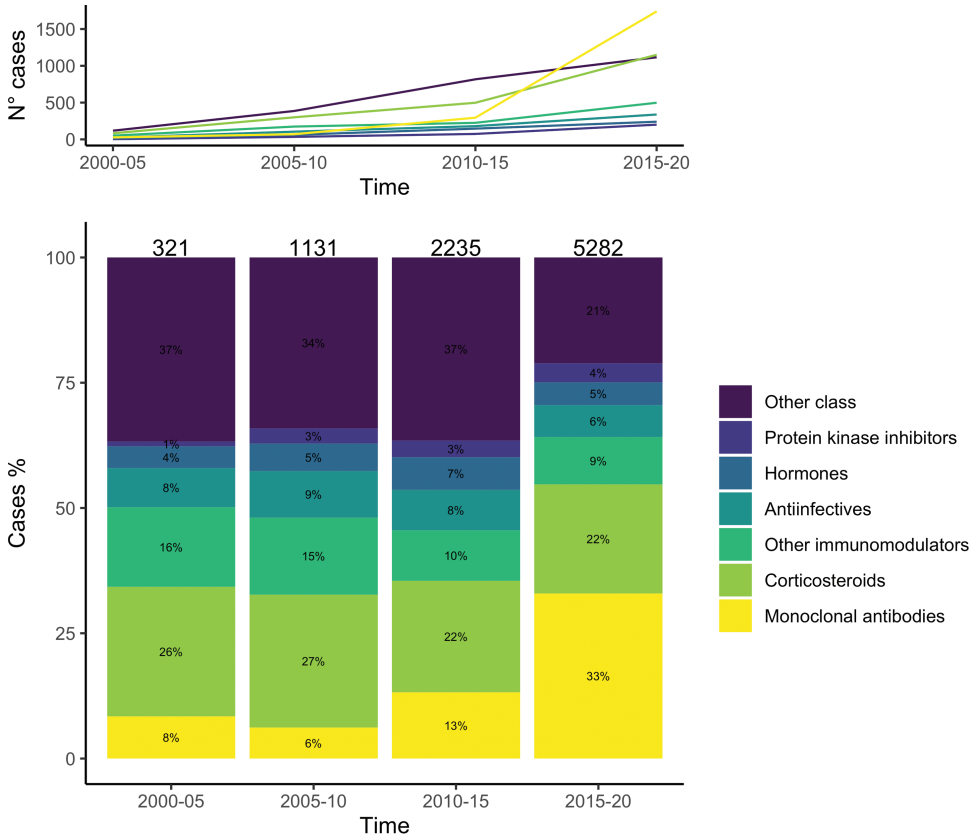

Figure 1. Evolution of cumulative number of reports (cases of adrenal hypofunctions for a given pharmacological class/total cases of adrenal hypofunction per year) by reporting year. The timeline is shown as half-decade, with the first one comprising only the period 2004 to 2005.

taking oral and intra-articular long-acting formulations, high glucocorticoid doses, and long treatment regimens (15, 16). Nevertheless, the risk of glucocorticoid-induced AI cannot be safely ruled out even in patients taking topical or inhaled glucocorticoids (17). The clinical and biochemical picture of AI may range from electrolyte imbalance, fatigue, hypoglycemia, gastrointestinal discomfort (abdominal pain, nausea, and vomiting), postural hypotension, and susceptibility to infections, up to acute circulatory collapse and death. The symptoms of AI occur more frequently within a few weeks after glucocorticoid withdrawal, although hypotension, gastrointestinal discomfort, and hypoglycemia may persist several months after withdrawal (18). Additionally, on reduction of high-dose corticosteroids or even under adequate glucocorticoid withdrawal regimens, patients may present with symptoms resembling those of AI, including anorexia, lethargy, myalgia, joint pain, and psychiatric disturbances (19). The so-called glucocorticoid withdrawal syndrome often leads to unnecessary supraphysiological doses of glucocorticoids to relieve the symptoms.

Glucocorticoid-induced AI is explained by 2 mechanisms: i) glucocorticoids suppress the HPA axis through the inhibition of the hypothalamic corticotropin-releasing-hormone and the pituitary adrenocorticotropin (ACTH) production; and ii) the lack of trophic stimuli by the ACTH to the adrenal gland eventually leads to adrenal gland atrophy, contributing to the occurrence of AI.

Even though treatment regimens, route of administration, potency, dose, duration of glucocorticoid treatment, as well as individual glucocorticoid sensitivity, have been postulated as potential risk factors for glucocorticoid-induced AI, no clear-cut predictive factors of risk of onset and duration of AI before HPA axis recovery have been identified so far (15, 16, 20, 21). The main reasons explaining this uncertainty are the lack of reliable data (studies with different design, populations, and treatment regimens) and the absence of guidelines on glucocorticoid-induced AI, leading to heterogeneous glucocorticoid withdrawal plans and different assessment of HPA axis recovery among studies (17, 22).

The finding of an unchanged proportion of AI related to glucocorticoid use over the last 20 years, ranging from 22% to 27% in each 5-year time frame, is worrisome. These data should increase awareness by physicians about the life-threatening nature of this condition. Of note, we found a large proportion of serious AI reports, including adrenal crisis, leading to hospitalization in 27.0% and death in 3.6% of the cases. According to a previous report, it is noteworthy that the incidence of adrenal crisis precipitated by infections and after reduction or discontinuation of glucocorticoid treatment was higher than that of patients with AI by other causes (23).

Regarding ICIs, patients receiving these monoclonal antibodies may experience a unique set of toxicities, the so-called irAEs, which can virtually affect any organ or tissue. Endocrine irAEs can be life-threatening with variegate chronic and unresolved dysfunctions involving the thyroid (hypothyroidism or thyrotoxicosis), pituitary (hypophysitis), adrenal glands (AI), and pancreas (diabetes mellitus) (24). While hypothyroidism and thyrotoxicosis have been mainly associated with anti-PD1/PDL1 agents (especially in a combination

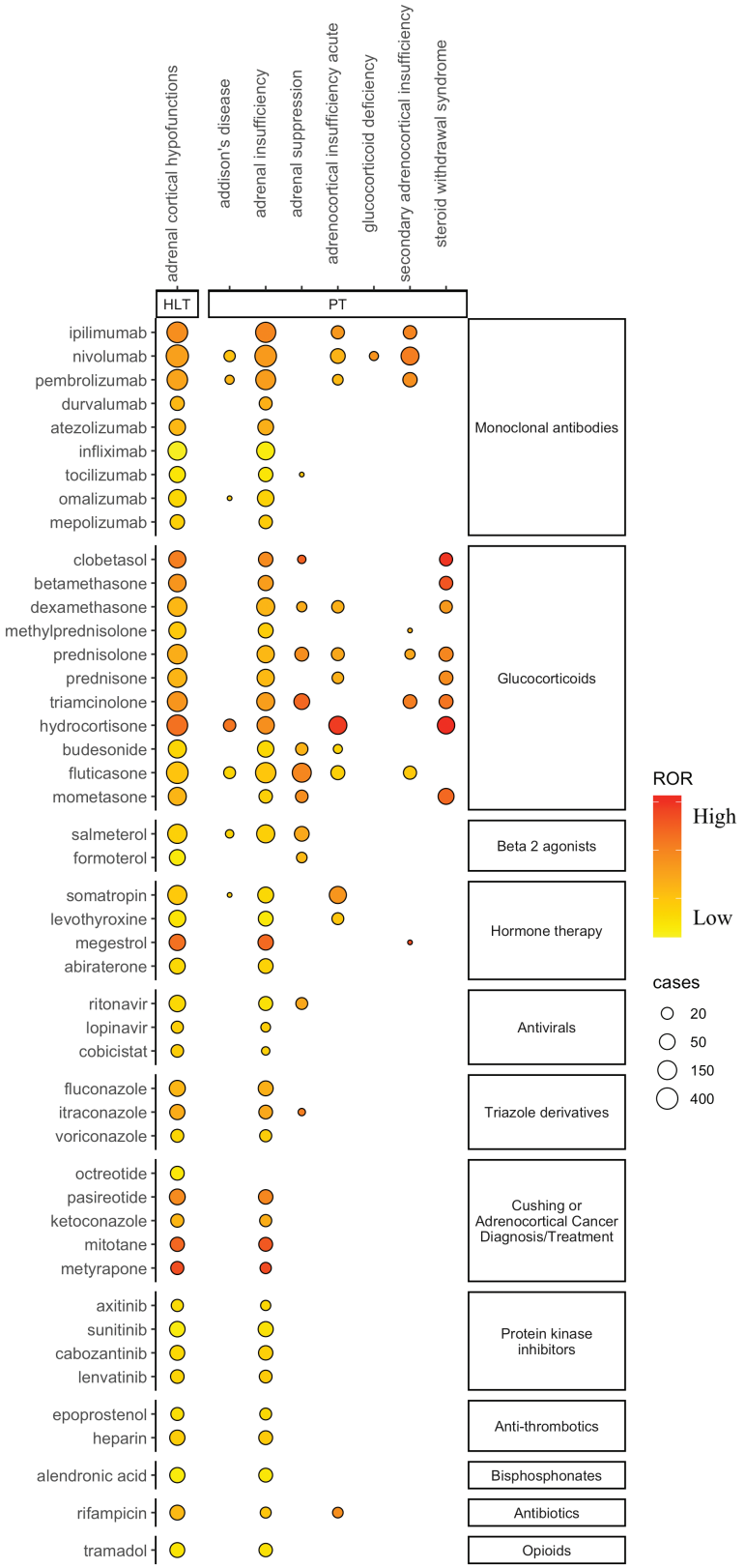

Figure 2. Heat map (disproportionality analysis). Drugs with statistically significant disproportionality reported in at least 20 cases as primary suspect are shown. The size of the circles is proportional to the number of cases.

regimen with anti-CTLA4, co-occurring with hepatobiliary and respiratory irAEs), hypophysitis, AI, and hypopituitarism were more frequently reported with anti-CTLA4 drugs (ipilimumab) (25, 26). Although toxic deaths are rare (27), endocrine irAEs (especially AI) can be life-threatening, and our data found a remarkable proportion of hospitalization,

life-threatening events, and death (54%, 12%, and 12% of the cases, respectively).

The occurrence of AI in ICI users has been reported in about 1% of cases and more frequently in individuals receiving combination regimens like anti-CTLA4 plus anti-PD1/PD-L1 agents (4%-8%) (25, 28, 29). Among the different ICIs, AI has been reported on treatment with nivolumab, pembrolizumab, and ipilimumab (30), with a median onset of 10 weeks for primary AI according to a scoping review of cases reports (range, 1.5-36) (31). Our data are in line with these findings (77 days as median onset; data not shown).

The plausible mechanisms underlying the development of AI by ICIs are adrenal hypofunction (primary AI) or pituitary ACTH deficiency (secondary AI). Primary AI is related to an immune destruction of the adrenal glands consequent to a hyperstimulation of the immune system due to ICIs mechanism of action. It has been linked to antiadrenal antibodies (32, 33), while atrophy of the glands has been reported as well (33). Adrenal inflammation highlighted with FDG-PET scan has been reported in several studies with both glands appearing hypermetabolic (34, 35). Similarly, secondary AI is related to a lymphocytic infiltration of the pituitary gland. ACTH deficiency was reported to persist in 86%-100% of patients, leading to the need for chronic hormone replacement therapy (30).

The net increase in reports of AI in patients under ICIs depicted in our study is consistent with the widespread and increasing use of those drugs during recent years (36). With the current development of combination therapies, including the association with vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors such as axitinib and cabozantinib, the reporting of AI should be tightly monitored (37). The signal of adrenal damage by anti-VEGF therapies in our study corroborated recent cases series (38) and is explained by the high expression of VEGFR-2 in the fenestrated capillaries of endocrine organs (39).

The recognition of AI in a patient under ICIs treatment is challenging, since the clinical presentation and the biochemical alterations consist of generic symptoms and electrolyte imbalances that may be common in patients with cancer (40). Therefore, in an oncological setting, the real prevalence of AI, when suspected based on clinical grounds, may be underestimated. Apart from the diagnosis, the management of ICIs-induced AI poses additional challenges, including the potential contributing role of comedications affecting pituitary function (eg, opioids) and ICI interruption until the patient is stabilized on replacement hormone (hydrocortisone and potentially fludrocortisone). Therefore, the latest American Society of Clinical Oncology guidelines recommended endocrine consultation for all grades of primary AI (41).

The proportion of reports of AI with the remaining drug classes is less worrisome and confirmed previous evidence on hormone therapy (abiraterone, somatotropin, levothyroxine) (2, 42), triazole antifungals (a likely class effect) (43), antiretrovirals (through impaired cortisol metabolism by cytochrome P4503A4 isozyme disruption) (44, 45), opioids (due to HPA axis suppression) (46, 47), and heparin (thrombocytopenia-mediated adrenal hemorrhage) (48). To the best of our knowledge, AI with alendronic acid is not described in the literature. A single case report recently documented adrenal crisis in a patient with Addison disease after the first intravenous infusion of zoledronic acid for osteoporosis (switch from denosumab) (49). Although biological plausibility remains uncertain, the contributing role of bisphosphonates in AI deserves further investigations of drug- and patient-related risk factors.

We acknowledge limitations of this study, including traditional drawbacks of pharmacovigilance research, such as the inability to infer causality (ROR is not a risk measure), quality of information (eg, laboratory and other clinical elements to validate the diagnosis), and lack of denominators, which does not allow us to calculate incidence rates. The observed increased reporting over time may be ascribable, at least partially, to a) missing data, especially for FDA date before 2010; b) the mandatory requirement of reporting AEs from clinical trials, especially serious unexpected events; c) an overall emerging awareness by reporters, especially consumers; and d) the increasing approvals and expanding indications of anticancer drugs in recent years. However, we observed a specific, steady increase in the proportion of adrenal hypofunctions reports (vs other reports), especially for ICIs in the 2015 to 2020 period. In addition, the disproportionality analysis may be subjected to reporting biases over time, including underreporting and stimulated reporting due to the influence of safety alerts or recent market approval, the so-called notoriety bias and Weber effect, respectively. Moreover, since disproportionality measures are interdependent, the lack of disproportionality should not be automatically interpreted as a safety endorsement. Several factors may influence the reporting pattern and relevant ability to detect disproportionality, including known and largely reported drug-event combinations (the so-called competition bias); tolerability profile (and pharmacodynamics); the setting, pattern, and extent of use (hospital vs community, short vs long term); as well as the attitude of clinicians toward reporting. This may explain the lack of statistically significant disproportionality for morphine (24 cases, ROR = 1.33; 95% CI, 0.85-1.99). However, our primary intent was not to primarily identify or characterize known and novel associations, but rather to describe the evolving spectrum of drug-induced AI over decades, focusing on the past 5 years. The modern FAERS reporting (after 2000) is not substantially influenced by the aforementioned reporting biases (50, 51), and the added value of pharmacovigilance studies has already been demonstrated in various settings (3, 4, 7, 8). Moreover, the expected underreporting further strengthens the need to increase physicians' awareness of a potentially overlooked safety issue. Our study shed light on the "tip of the iceberg," namely clinically relevant cases with serious outcomes, such as hospitalization and death. Furthermore, we applied a threshold of 10 cases and the Bonferroni correction to minimize the detection of spurious associations and avoid (unjustified) alarm. In this regard, we also excluded a priori signs/symptoms with low specificity (eg, fatigue, hypotension), thus making misclassification of cases unlikely. We also acknowledge that several patients might have received multiple medications potentially affecting adrenal function; this prompted us in restricting a priori the analysis only to drugs recorded as suspect.

Conclusions

We describe a heterogeneous spectrum of drugs reported to impair adrenal function comprising, among others, topical and systemic glucocorticoids and immunotherapy. These findings should raise the awareness of drug-induced AI as a current clinically relevant issue, involving patients and treating physicians among different medical specialties.

Therefore, we call for a) dedicated screening programs for early identifications and treatment of AI in the rapidly expanding group of patients under ICI treatment; and b) structured educational programs for patients taking drugs potentially inducing AI and their caregivers, who should be informed about potential risks and management of this condition in the chronic setting and during acute adrenal crisis.

Finally, we believe that our study is a claim for an urgent identification of predictive factors for glucocorticoid-induced AI, derived from targeted pharmacokinetic studies, and reliable regimens of glucocorticoid withdrawal, to avoid clinically relevant AI.

Disclosures

The authors have nothing to disclose.

Data Availability

The data sets analyzed in the present study are publicly available (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html, accessed March 9, 2022). Codes for the analyses are available on reasonable request to the authors.

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