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Concomitant medications during immune checkpoint blockage in cancer patients: Novel insights in this emerging clinical scenario

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ABSTRACT

The use of immune checkpoint inhibitors (ICIs) in cancer patients is rapidly growing. However, the potential impact of some widely used concomitant medications is still largely unclear. Emerging data suggest that gut microbiota may affect the efficacy of ICIs, leading to the hypothesis that concurrent antibiotics and proton pump inhibitors use could have a detrimental effect. In addition, steroid use might potentially impair the activity of immunotherapy, due its known immunosuppressive effects, and some safety concerns have been raised in patients receiving commonly used vaccination during ICIs. However, all randomized trials evaluating ICIs consistently excluded patients receiving high corticosteroid doses and data regarding other concomitant medications are lacking. Recently, several retrospective studies have tried to address this unmet medical need. Herein we discuss the latest evidence on the influence of these medications, critically analyzing the data reported so far and the possible implications in our clinical practice.

1. Introduction

Immune checkpoint inhibitors (ICIs) targeting Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) and programed death-1/programmed death ligand-1 (PD-(L)1) pathways have revolutionized the therapeutic management of several solid tumors, with unprecedented effects on overall survival (OS). These major breakthroughs are highlighted by the 2018 Nobel Prize in Physiology or Medicine awarded to James P. Allison and Tasuku Honjo for the discovery of these proteins and their blockage as an anticancer treatment. Since their discovery over a decade ago, ICI indications continue to expand, posing new challenges in clinical practice due to interactions with concomitant medications. Indeed, all the pivotal clinical trials with these drugs have excluded patients using corticosteroids (i.e. prednisone ≥10 mg daily). Additionally, most clinical trials do not report efficacy or safety data regarding the impact of concomitant use of ICIs with commonly used drugs in clinical practice, such as antibiotics and proton pump inhibitors (PPIs) that may affect the activity of these compounds through the alteration of gut microbiota. Moreover, the prophylactic use of vaccines is common in cancer patients in order to prevent infectious complications resulting from the immune suppressive effects associated with conventional cancer treatments, such as chemotherapy and radiotherapy. However, the use of simultaneous medications in cancer patients treated with immunotherapy is not well studied.

In this paper we provide a comprehensive overview on the role of different concomitant medications that may influence the therapeutic efficacy and/or safety of ICIs, including corticosteroids, antibiotics, vaccines, and proton pump inhibitors to address an unmet need in this growing complex clinical scenario.

2. Corticosteroid use and immune checkpoint inhibitors

Since the dawn of the immunotherapy era, corticosteroid therapy has been considered as the antidote of possible side effects, capable of

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Table 1
Retrospective studies evaluating the impact of early steroid use on ICIs efficacy.

Study	Cancer type (n)	ICIs used	Window of steroid use respective to ICI start	Early steroid users	ORR (%) Early steroid vs. No steroid	PFS (mos) Early steroid vs. No steroid	OS (mos) Early steroid vs. No steroid
Scott and Pennell, 2018	NSCLC (210)	PD-1 inhibitor	Within 1 month	12%	N.A.	N.A.	4.3 vs. 11.0 ($p=0.017$)
Arbour et al., 2018	NSCLC (640)	PD(L)-1 inhibitors	At the beginning	14%	7 vs. 18 ($p < 0.005$)	N.A. v.s N.A. ($p < 0.001$)	N.A. v.s N.A. ($p < 0.001$)
Fucà et al., 2019	NSCLC (151)	PD(L)-1 inhibitors (plus a CTLA-4 inhibitor in 4%)	Within 1 month	23%	17 vs. 24% ($p=0.39$)	1.98 vs. 3.94 ($p=0.003$)	4.86 vs. 15.14 ($p < 0.001$)
Ricciuti et al., 2019	NSCLC (650)	PD(L)-1 inhibitors +/- CTLA-4 inhibitor	Within 24 hours of the first dose of the PD(L)-1 inhibitor	14.3%	6.1* vs. 22.2** vs. 19.7($p=0.01$)	1.4* vs. 4.6** vs. 3.4 ($p < 0.01$ and $p=0.24$)	2.2* vs. 10.7** vs. 11.2 ($p=0.001$ and $p=0.77$)

Legend: NSCLC, non small cell lung cancer; ORR, overall response rate; PFS, progression free survival; OS, overall survival; ICIs, immune checkpoint inhibitors; N.A. not available.

* Prednisone ≥10 mg/d for cancer-related palliation.

** Prednisone ≥10 mg/d for cancer-unrelated indications.

extinguishing immune-related adverse reactions (irAEs). On the hypothesis that corticosteroid use could reduce the efficacy of immunotherapeutic drugs, most registrative trials have considered concomitant treatment with prednisone doses above 10 mg or equivalent as an exclusion criterion. For this reason there is no prospective data from randomized trials to evaluate the impact of corticosteroids on the efficacy of ICIs. Recently several retrospective studies have investigated potential interferences between early corticosteroid use and immunotherapy [Table 1].

The first study published by Arbour et al. analyzed 640 NSCLC patients treated with anti-PD(L)1 agents at two Institutions: The Memorial Sloan Kettering Cancer Center (MSKCC; 455) and the Goustave Roussy Cancer Center (GRCC; 185). In this study, 90 patients (14%) had been treated with prednisone ≥10 mg prior to beginning treatment with an ICI. The analysis evaluated the progression free survival (PFS), OS and overall response rate (ORR) of these patients. A multivariate analysis was conducted with adjustments for smoking status, Easter Cooperative Oncology Group (ECOG) performance status and presence of brain metastasis. The results of the study showed that the use of corticosteroids at the beginning of therapy with anti-PD(L)1 was associated with worse outcomes, including shorter PFS (HR 1.3, $p < 0.03$), shorter OS (HR 1.7, $p < 0.001$), and lower ORR (7% vs. 18%, $p < 0.005$). Considering the two cohorts separately, the differences were more pronounced in the MSKCC cohort than GRCC (median PFS of 1.9 months vs. 2.6 months; HR 1.7; $p=0.001$), which also included patients who were taking corticosteroids within 30 days of starting therapy (Arbour et al., 2018).

Second, a retrospective study conducted at the Cleveland clinic included 210 NSCLC patients of whom 66 (31%) received corticosteroids equivalent to a prednisone dose of 10 mg daily with concomitant ICI and 25 (12%) had an early exposure to corticosteroids (within the first 30 days of ICI treatment). The median OS for patients with an early concomitant treatment with corticosteroids was 4 months compared with 11 months in those who did not receive corticosteroids (HR 2.30, 95% CI 1.27–4.16, $p=0.006$) in a multivariate analysis, considering sex, age, smoking status, histology type, time from diagnosis, ECOG PS, and prior brain metastases. Among 31 patients who required corticosteroids for the treatment of irAEs, there was no statistically significant difference in terms of OS when compared to patients without irAEs (16.1 versus 10.5 months; 95% CI: 8.6–12.2, $p=0.50$) (Scott and Pennell, 2018).

A third retrospective analysis included 151 NSCLC patients treated at the Fondazione IRCCS Istituto Nazionale dei Tumori di Milano. This study analyzed patients treated with corticosteroids (prednisone-equivalent dose ≥ 10 mg) for at least 1 day within 28 days from the start of ICIs. Early corticosteroid exposure was observed in 35 patients (23%) and was significantly associated with lower disease control rate (DCR) (OR 0.32, $p=0.006$), shorter PFS (HR 1.80, $p=0.003$), and shorter OS (HR 2.60, $p < 0.001$). A modulation of peripheral blood immune cells was also noted, which may have contributed to the lower antitumor response (Fucà et al., 2019).

Collectively, these studies have strong biological plausibility and available data suggests that starting corticosteroids during immunotherapy for the management of irAEs does not compromise its efficacy, as shown in different clinical settings with both anti-CTLA4 (Horvat et al., 2015) and anti–PD(L1) agents (von Pawel et al., 2017) (Leighl et al., 2015). However, the conclusions from these studies are not warranted: It was correctly acknowledged that their studies could not distinguish the prognostic and predictive effects of corticosteroids in these patients. In all of these studies corticosteroid treatment before or within 30 days from starting ICIs was associated with patients' characteristics usually associated with a worse prognosis (higher ECOG PS, baseline brain metastases, chronic obstructive pulmonary disease, higher metastatic sites) (Arbour et al., 2018) (Scott and Pennell, 2018) (Fucà et al., 2019). For this reason they performed multivariate analyses to minimize confounding effects of these factors.

The prognostic role of corticosteroid use was already studied with chemotherapy and a systematic review showed that the use of glucocorticoids might be deleterious in lung cancer patients (Keith, 2008). Moreover, the fact that the association between baseline corticosteroids and prognosis persisted after multivariate adjustments for known prognostic factors is insufficient to prove that there is a true cause-effect relationship, for 2 reasons:

1 When a strong prognostic factor (like as ECOG PS) shows a large difference in distribution between the groups being compared (in this case corticosteroids users and non-users), adjustment that uses classes of the factor may not be sufficient to entirely remove its confounding effect. This phenomenon, referred to as intraclass (or residual) confounding, is well known to epidemiologists (Fewell et al., 2007) and may cause spurious associations of considerable size in multivariate analyses in observational studies. In this case, we postulate that multivariate analyses could not completely adjust away the differences in the distribution of ECOG PS and in the frequency and clinical impact of brain metastases between corticosteroid users and non-users. For instance, it is conceivable that patients with brain metastases who were taking corticosteroids had more serious symptoms than patients with brain metastases who were not taking corticosteroids (Scott and Pennell, 2018).
2 It is also plausible that the use of corticosteroids at the time of the initiation of immunotherapy had the effect of improving the clinical condition of several patients, thereby "downgrading" their ECOG PS. As a consequence, these patients had a more aggressive disease and a worse prognosis than patients assigned to the same ECOG PS

Table 2
Retrospective studies evaluating the impact of antibiotics prescription in patients treated with immune checkpoint inhibitors.

Study	Cancer type(s) (n)	ICIs used	ATB window respective to ICIs start	ATB + patients	ORR (%) ATB- vs. ATB+	PFS (mos) ATB- vs. ATB+	OS (mos) ATB- vs. ATB+
Routy et al., 2018	NSCLC (140), RCC (67), UC (32)	PD(L)-1 inhibitors	Within 2 months before and 1 month after	28%	N.A.	4.1 vs. 3.5 ($p = 0.017$)	20.6 vs. 11.5 ($p < 0.001$)
Derosa et al., 2018a	RCC (121) NSCLC (249)	PD(L)1 +/- CTLA-4 inhibitors or bevacizumab	Within 1 month before	13% (RCC)	26 vs. 13 ($p < 0.01$) (RCC)	7.4 vs. 1.9 ($p < 0.01$) (RCC)	30.6 vs. 7.3 months ($p = 0.03$) (RCC)
				20% (NSCLC)	23 vs. 13 ($p < 0.01$) (NSCLC)	3.8 vs. 1.9 ($p = 0.03$) (NSCLC)	24.6 vs. 7.9 ($p < 0.01$) (NSCLC)
Huemer et al., 2018	NSCLC (30)	PD-1 inhibitors	Within 1 month before and 1 month after	36.7%	N.A.	3.1 vs. 2.9 ($p = 0.031$)	15.1 vs. 7.5 ($p = 0.026$).
Kaderbhai et al., 2017	NSCLC (74)	PD-1 inhibitors	Within 3 months before and during ICI therapy	20.3%	22 vs. 26.7 ($p = 0.75$)	*N.A. vs. N.A.* ($p = 0.72$)	N.A.
Elkrief et al., 2019	Melanoma (74)	PD-1 or CTLA-4 inhibitors	Within 1 month before	13.5%	34 vs. 0 ($p < 0.01$)	7.3 vs. 2.4 ($p = 0.01$)	18.3 vs. 10.7 ($p = 0.17$)
Lalani et al., 2018	RCC (146)	PD(L)1 +/- CTLA-4 inhibitors	Within 4 weeks before and 8 weeks after	21%	24.2 vs. 19.3 ($p = 0.005$)	8.1 vs. 2.6 ($p = 0.008$)	*N.A. vs. N.A.* ($p = 0.257$)
Tinsley et al., 2018	Melanoma (201), NSCLC (58), RCC (46)	ICIs	Within 2 weeks before and 6 weeks after	31%	N.A.	5.8 vs. 3.2 ($p = 0.049$)	21.4 vs. 10.4 ($p = 0.001$)
Do et al., 2018	NSCLC (109)	PD-1 inhibitors	Within 1 month before the first dose and 1 month after the last dose	79.8%	N.A.	N.A.	17.2 vs. 5.4 ($p = 0.0004$)
Hakozaki et al., 2019	NSCLC (90)	PD-1 inhibitors	Within 1 month before	14.4%	N.A.	4.4 vs. 1.2 ($p = 0.04$)	N.R. vs. 8.8 ($p = 0.037$)
Zhao et al., 2019	NSCLC (109)	PD-1 inhibitors +/ chemo or apatinib	Within 1 month before and 1 month after	18.3%	22.5 vs. 15 ($p = 0.092$)	9.6 vs. 3.7 ($p < 0.0001$)	21.9 vs. 6.1 ($p = 0.0021$)
Galli et al., 2019	NSCLC (157)	PD(L)-1 inhibitors	Within 1 month before and 3 months after	17.2%	11.1% vs. 24.6 ($p = 0.2018$)	3.3 vs. 2.2 ($p = 0.1772$)	5.9 vs. 11.9 ($p = 0.2492$)
Ouaknine et al., 2018	NSCLC (72)	PD-1 inhibitors	Within 2 months before and 1 month after	38.9%	*N.A. vs. N.A.* ($p = 0.276$)	3.3 vs. 2.8 ($p = 0.249$)	13.4 vs. 5.1 ($p = 0.027$)
Chalabi et al. 2018	NSCLC (757)	PD-L1 inhibitor	Within 1 month before and 1 month after	27%	N.A.	1.76 vs. 2.79 ($p = 0.08$)	8.54 vs. 14.06 ($p < 0.01$)
Pinato et al., 2019	NSCLC (119), Melanoma (38), others (39).	PD(L)-1 inhibitors	Within 1 month before and concurrently	15%	N.A.	N.A.	($p < 0.001$) (pATB) ($p = 0.76$) (cATB)

Legend: N.R. not reached; N.A. not available; NSCLC, non small cell lung cancer; RCC, renal cell carcinoma; UC, urothelial carcinoma; ATB+, patients treated with antibiotics; ATB-, patients who did not received antibiotics; ORR, overall response rate; PFS, progression free survival; OS, overall survival; ICIs, immune checkpoint inhibitors; pATB, prior antibiotic use; cATB, concurrent antibiotic use.

class who were not taking corticosteroids; independent of any negative effect of corticosteroids.

Even these potential biases do not proof that the observed association between baseline corticosteroid use and response/prognosis in NSCLC patients receiving ICI is fortuitous, lead to generate this hypothesis. A retrospective study recently published by Ricciuti et al *(Ricciuti et al. Immune Checkpoint Inhibitor Outcomes for Patients With Non–Small-Cell Lung Cancer Receiving Baseline Corticosteroids for Palliative versus Nonpalliative Indications)* showed that the worse outcome observed among patients who received ≥10 mg of prednisone seems related to the specific poor prognosis subgroup. Infact, there was no significant difference in PFS or OS in patients receiving ≥10 mg of prednisone for cancer-unrelated indications. In conclusion, theproof can derive only from properly conducted subgroup analyses of already conducted randomized trials comparing ICIs to chemotherapy in NSCLC (and in other cancers, as well) or from new randomized trials. Meanwhile, the management of NSCLC patients who are candidates for ICIs and are receiving corticosteroids should not be affected by the results of these studies.

3. Antibiotics use and ICIs

Antibiotics (ATBs) represent a frequent concurrent treatment during immunotherapy and were shown to alter gut microbiota leading to dysbiosis and associated with inflammatory conditions (Francino, 2016) and influence immune responses (Ubeda and Pamer, 2012). Furthermore, it has been demonstrated that gut microbiota is able to exert a significant influence on response to ICIs (Sivan et al., 2015) (Pitt et al., 2016) (Gopalakrishnan et al., 2017) (Chaput et al., 2017).

The first evidence to demonstrate the influences of antibiotics on gut microbiota during ICIs comes from preclinical studies in both *in vitro* and *in vivo* models. Vétizou et al. tested the effects of CTLA-4 blockade in mouse models in pathogen-free (SPF) and germ-free (GF) conditions and reported that both GF condition and treatment with antibiotics reduce anti-CTLA-4 anti-cancer activity, activation of splenic effector $CD4^+$ T cells, and Tumor-infiltrating lymphocytes (TILs). Antitumor effects of CTLA-4 blockade seems to depend on distinct Bacteroides species. Evidence from studies in mice and humans showed that T cell responses specific for B. thetaiotaomicron or B. fragilis were associated with the efficacy of CTLA-4 blockade. Bacteroides involvement during therapy with anti-CTLA-4 is partially explained by the T-helper 1 activation against B. fragilis capsular polysaccharides. In addition, human feces were analyzed before and after ipilimumab administration, identifying 3 major clusters: Cluster A rich in Alloprevotella or Prevotella, cluster B and cluster C, both rich in Bacteroides. Fecal transplantation into GF mice receiving anti-CTLA4 induced higher tumor-control rates in those mice receiving feces from cluster C. Tumor control rate was the same in mice that were found to be colonized by immunogenic B. fragilis and B. thetaiotaomicron. B. fragilis and in B. thetaiotaomicron colonization in antibiotic-treated mice reduced pathologic severity of CTLA-4-related colitis (Vetizou et al., 2015). This data suggests that immunotherapy is able to modify intestinal microbiota that in turn influences the response to immunotherapy itself.

Colitis is a frequent irAE seen in anti-CTLA-4 treatment (Freeman,

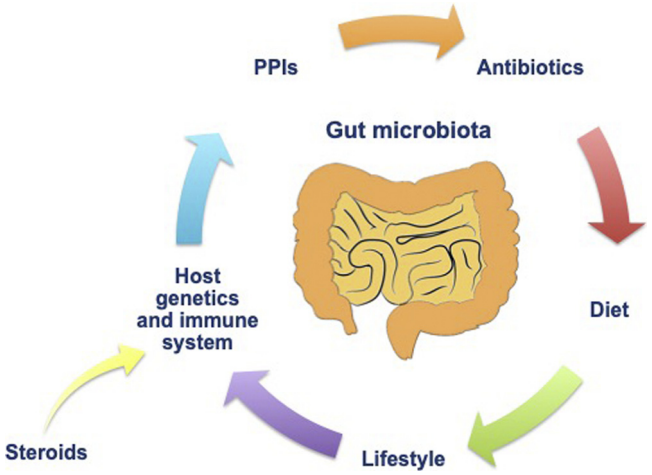

Fig. 1. Multiple factors influencing gut microbiota composition.

2012). Bifidobacterium has been reported to mitigate immune-related colitis in the context of CTLA-4 blockade in a mouse colitis model, likely modulating the metabolic functions of T regulatory cells (T_{regs}) that are key actors in auto-immunity induction mechanisms, without affecting their number. Moreover, this data supports the use of caution in case of concomitant use of ATB during CTLA-4 blockage, as commonly used antibiotics, such vancomycin, inhibit Bifidobacterium species (Wang et al., 2017). Recently, promising data was reported in a preliminary study of patients with refractory immune checkpoint inhibitor-associated colitis successfully treated with fecal microbiota transplantation, with reconstitution of the gut microbiome and a relative increase in the proportion of T_{regs} within the colonic mucosa (Wang et al., 2018).

The composition and heterogeneity of gut microbiota plays a pivotal role in providing a robust immune defense (Geva-Zatorsky et al., 2017) and may influence the efficacy of ICIs targeting PD(L)-1 and CTLA-4 as recently reported by Routy et al. showing that primary resistance to these agents can be attributed to abnormal gut microbiome composition. The use of ATB inhibited the clinical benefits of ICIs in patients with advanced cancer. However, fecal microbiota transplantation from cancer patients who responded to ICIs into GF or ATB-treated mice ameliorated the antitumor effects of PD-1 blockade, although not for nonresponding patients. Metagenomics analyses of patient stool samples at diagnosis revealed correlations between clinical responses to ICIs and the relative abundance of Akkermansia muciniphila. A higher concentration in E. hirae was also detected in feces of patients with NSCLC responding to ICIs in comparison to non-responders (Routy et al., 2018).

Based on this preclinical data, several retrospective studies evaluated the impact of ATB use in patients treated with ICIs [Table 2].

These studies included different patient populations both in terms of tumor histology (mostly NSCLC, RCC and melanoma) and different ATB use windows. However, the vast majority investigated the role of early ATB use (before 1–2 months and 1 month after the start of immunotherapy) [Table 2]. Most of these studies have investigated the impact of ATB use on ICIs targeting PD(L)-1 (Huemer et al., 2018) (Zhao et al., 2019) (Routy et al., 2018) (Kaderbhai et al., 2017) (Do et al., 2018) (Hakozaki et al. 2018) (Galli et al., 2019) (Ouaknine et al., 2018) (Chalabi et al., 2018) (Pinato et al., 2019) albeit some studies have also included patients treated with anti-CTLA4 agents either alone or in combinations (Sen et al., 2018) (Elkrief et al., 2019) (Derosa et al., 2018a,b) (Lalani et al., 2018).

Collectively, these studies suggest that ATB use has a negative impact on outcomes in patients receiving immune checkpoint inhibitors in terms of ORR (Elkrief et al., 2019) (Derosa et al., 2018a,b) (Lalani et al., 2018), PFS (Elkrief et al., 2019) (Derosa et al., 2018a,b) (Lalani et al., 2018) (Routy et al., 2018) (Huemer et al., 2018) (Zhao et al., 2019) (Tinsley et al., 2018) (Hakozaki et al., 2019) (Chalabi et al., 2018), and OS (Huemer et al., 2018) (Zhao et al., 2019) (Routy et al., 2018) (Do et al., 2018) (Hakozaki et al., 2019) (Ouaknine et al., 2018) (Chalabi et al., 2018) (Pinato et al., 2019) (Derosa et al., 2018a,b) (Tinsley et al., 2018). The hypothesis emerging from these studies is that the ATB-related dysbiosis might decrease the diversity of gut microbiota thereby eliminating the most immunogenic bacteria (Derosa et al., 2018a,b). Gut and blood microbiota profiling studies could help to predict the efficacy of ICIs and to evaluate the impact of different bacteria species on the outcome of these patients. Recently, in a preliminary study, it was reported that early ATB use influenced plasma citrulline levels, an amino-acid produced entirely by enterocytes, independently of nutritional status. Citrulline is a validated marker of intestinal barrier and enterocytes function and plasma levels have been correlated in NSCLC patients treated with nivolumab with clinical benefit, PFS and OS (Ouaknine et al., 2018). Moreover, as reported in some of these studies, the route of antibiotic administration might influence the efficacy of ICIs. Receiving ATB intravenously seems to be associated with worse survival outcomes (Mielgo-Rubio et al., 2018). The type of infection treated with ATBs is also important as patients with lower respiratory tract infections and urinary infections appear to have poorer outcomes (Mielgo-Rubio et al., 2018). The spectrum of activity of ATBs used may also influence ICI efficacy (Ahmed et al., 2018), albeit these differences may be associated with sicker patients requiring hospitalization and with a poor performance status. Interestingly, a recent retrospective analysis suggested that prior ATB use within one month from ICI start is associated with worse OS, but not the concomitant use. This negative impact on survival was independent of histotype, tumor burden, and ECOG PS (Pinato et al., 2019).

Prospective studies are needed to better define the optimal ATB window, the differences in ATB classes, the route of administration, the duration of ATB therapy, and the potential impact of other concomitant medications and conditions that might alter the microbiome, such PPI use, corticosteroid use and the diet composition [Fig. 1]. Therefore, in the absence of clear evidence, the use of ATBs, especially for long or repeated courses, during immunotherapy should be carefully evaluated. However, the use of ATB still remains mandatory in cases of bacterial infectious diseases. Further, opportunistic infections that may emerge in cases of immune depression, as observed in patients requiring prolonged corticosteroid therapies as for severe irAEs.

4. Proton pump inhibitors and immunotherapy

Proton pump inhibitors (PPIs) are in widespread use for multiple indications including gastro-esophageal reflux disease and prevention and treatment of peptic ulcer disease. They are now some of the most frequently prescribed drugs throughout the world, with large numbers of patients provided ongoing treatment with PPIs administration for several years (Lanas, 2016). Potent gastric acid suppression using PPIs has important effects on human health that are mediated through changes in the gastrointestinal microbiome (Chen et al., 2016) (Cárcer et al., 2010). PPIs inhibit gastric acid secretion by blocking hydrogen/potassium ($H+/K+$) ATPases in gastric parietal cells and cause an increase of the intragastric PH, which may perturb microbial communes, leading to dysbiosis and an increased risk of enteric infection and diarrhea in humans (Malfertheiner et al., 2017) (Magalhães et al., 2005) (Leonard et al., 2007). Several retrospectives studies have shown that PPI use increases the risk of enteric infections, such as *Clostridium difficile and Campylobacter*, as well as community-acquired pneumonia (Freedberg et al., 2014) (Lombardo et al., 2010) and also increase the incidence of small intestinal bacterial overgrowth (Lombardo et al., 2010) (Jackson et al., 2015) (Clooney et al., 2016). PPI use has been associated in clinical studies with a decreased diversity of the gut microbiome as compared to non-users (Imhann et al., 2015) and significant changes in the gut microbiome composition during PPI treatment (increase of Lactobacillus species and Streptococcus species at 4

Table 3
Impact of PPI use on the therapeutic efficacy of ICIs in patients with solid tumors.

Study	Cancer type(s) (n)	ICIs used	Type of PPI	PPI window respective to ICIs start	PPI users patients	ORR (%) PPI users vs. non users	PFS (mos) PPI users vs. non users	OS (mos) PPI users vs. non users
Routy et al., 2018	NSCLC (140), RCC (67), UC (32)	PD(L)-1 inhibitors	Not specified	Within 2 months before and 1 month after	N.A.	N.A.	3.8 vs. 4.0 ($p = 0.431$)	13.1 vs. 19.0 ($p = 0.285$)
Hakozaki et al., 2019	NSCLC (90)	PD-1 inhibitors	Not specified	Within 1 month before	19%*	N.A.	N.A.	8.8 vs. NR ($p = 0.04$)
Zhao et al., 2019	NSCLC (109)	PD-1 inhibitors +/ chemo or apatinib	Not specified	Within 1 month before and 1 month after	36.5%	27.5 vs.17.4 ($p = 0.213$)	9.63 vs. 6.23 ($p = 0.343$)	11.9 vs. 23.7 ($p = 0.754$)
Mukherjee et al., 2018	Melanoma (33), NSCLC (28), Other (97)	PD(L)-1 inhibitors	Not specified	Concomitant use	46.2%	N.A.	4.9 vs. 3.4 ($p = 0.77$)	NE vs. NE ($p = 0.77$)
Chalabi et al., 2018	NSCLC (757)	Atezolizumab	Not specified	Within 1 month before and 1 month after	31%	N.A.	1.89 vs. 2.83 ($p < 0.01$)	9.63 vs. 14.52 ($p < 0.01$)

Legend: N.R. not reached; N.A. not available; NSCLC, non small cell lung cancer; RCC, renal cell carcinoma; UC, urothelial carcinoma; PPI, proton pump inhibitor; ORR, overall response rate; PFS, progression free survival; OS, overall survival; ICIs, immune checkpoint inhibitors.
* included also patients receiving H_2Bs (histamine H_2-blockers).

and 8 weeks compared with counts before treatment (Hojo et al., 2018) that might predispose patients to dysbiosis and enteric infections.

Given the increasing importance attributed to gut microbiome in the efficacy of ICIs with the enrichment of particular bacteria species in responding patients and a possible detrimental effect of the ATB use, studies have investigated the potential effect of PPI use in cancer patients treated with these inhibitors. However, only a few studies have been reported to date, with conflicting results [Table 3].

Some retrospective studies have reported no statistically significant differences in the clinical activity of ICIs in different solid tumors both in terms of PFS and OS (Mukherjee et al., 2018) (Routy et al., 2018) (Zhao et al., 2019), and irAEs frequency (Mukherjee et al., 2018) between PPI users and non-users. In contrast, a pooled analysis (1512 patients) of the phase II/III trials OAK and POPLAR, comparing the anti-PDL1 agent atezolizumab with docetaxel in pretreated NSCLC patients, reported shorter PFS and OS in PPI users compared to non-users treated with atezolizumab in both univariate ($p < 0.01$ for both PFS and OS) and multivariate analyses ($p = 0.02$ and $p < 0.01$, respectively) (Chalabi et al., 2018). In addition, a small retrospective Japanese study reported a negative survival impact with the use of PPIs during ICI treatment in NSCLC ($p = 0.04$), although in multivariate analyses no statistically significant association was observed ($p = 0.15$) (Hakozaki et al., 2019).

These studies confirm the need to investigate potential roles of PPI use on primary resistance to ICIs and may provide rational for therapeutic strategies exploiting gut microbioma as a driver for immunotherapy activity. However, most of these studies are limited by small sample sizes and were conducted at single institutions. In addition, in all of these studies the type and dose of PPIs used as well as the compliance to PPI treatment were not assessed and might have significantly impacted gastric acid suppression. Moreover, only selected studies evaluated the effects of other concomitant medications that could potentially affect the gut microbiome and might have confounded to the effect of these agents on ICIs activity.

5. Vaccines and immunotherapy

PD-1 and its ligands PD-L1/PD-L2 are crucial for the maintenance of immune homeostasis through modulation of the duration and amplitude of physiological immune responses in peripheral tissues that occur during viral infections and inflammation and minimizing the T cell-mediated damage of normal tissues (Chen and Flies, 2013). Moreover, T cell dysfunction and relapses of viral infections are also involved in the complex pathway (Valero-Pacheco et al., 2013) (Erickson et al., 2012). The blockage of PD(L)-1 pathway increases cancer-specific immunity. However, virus-specific immunity is increased due to blockade of the PD-1 signaling cascade (Mcnally et al., 2013) (Dirks et al., 2012). Treatments with agents targeting the PD(L)-1 axis usually show a good safety profile with a low risk for grade 3–5 irAEs. While severe irAEs are an uncommon complications of anti-PD(L)-1 monotherapy, selected cases irAEs can be life-threatening (Hofmann et al., 2016).

Prevention of infection is crucial for individuals with impaired immunity. Viral infections in cancer patients often result in high morbidity and mortality rates that may reach 9% for influenza syndrome (IS) (Hibberd and Rubin, 1990) (Cooksley et al., 2005). It has been hypothesized that vaccine administration may result in exaggerated activation of the immune system in patients receiving ICIs (Wijn et al., 2018). Although it is impossible to identify whether irAEs were caused by influenza vaccine in several cases of fatal myositis, myocarditis and rhabdomyolysis in patients receiving ipilimumab, nivolumab and influenza vaccine. A recent prospective study of 23 patients receiving nivolumab or pembrolizumab and trivalent influenza vaccine found an increase in grade 3 to 4 irAEs (26.1%) compared to unvaccinated patients treated with these agents (Läubli et al., 2018). In the multicenter retrospective INVIDIa study the use of inluenza vaccine seemed less clinically effective in advanced cancer patients treated with ICIs, with a higher incidence of IS occurrence in vaccinated patients than for the non-vaccinated patients (24.1% vs. 11.8%, $p = 0.009$) and a more pronounced effect among the elderly ($p < 0.0001$). This phenomenon cannot be justified by vaccine-derived inluenza-like adverse reactions, because of the prolonged time frame from vaccine administration to IS occurrence and the unequivocal definition of IS. Interestingly, administration of flu vaccine did not negatively impact the efficacy of cancer immunotherapy. In some cases vaccination even correlated with better treatment efficacy (Bersanelli et al., 2018). Similar findings were reported in two retrospective studies evaluating ICIs in patients with NSCLC and melanoma (Läubli et al., 2018) (Schenk, 2017).

It has been hypothesized that the administration of vaccines to patients with cancer receiving immunotherapy might result in a higher incidence of vaccine-related adverse events or serious irAEs. The exact pathophysiological mechanism of irAEs after checkpoint blockade and how the breakdown of tolerance towards self-antigens occurs in patients with irAEs is not completely understood (June et al., 2017) (Tocheva and Mor, 2017). Most data is derived from preclinical models and correlative human studies. How the combination of prophylactic vaccination and PD-1 blockade could increase irAEs also remains speculative. The physiological role of the PD-1/PD-L1 pathway is to mediate peripheral tolerance of T cells and inhibition of immune checkpoints could break such tolerance (Dong and Chen, 2003).

In a small study including 23 patients with lung cancer patients and 11 age-matched healthy controls using a trivalent inactivated influenza

Table 4
Retrospective studies evaluating the impact of vaccination on safety and/or therapeutic efficacy in cancer patients treated with ICIs.

Study	Cancer type(s) (n)	ICIs used	Type of vaccine	Vaccinated patients	irAEs (%) Vaccinated vs. non-vaccinated	irAEs G3-4 (%) Vaccinated vs. non-vaccinated	OS (mos) Vaccinated vs. non-vaccinated
Bersanelli et al., 2018	NSCLC (103), RCC (112), melanoma (55), other (30)	PD(L)-1 inhibitors, CTLA-4 (< 1%)	Trivalent or quadrivalent inactivated influenza vaccine	26.3%	N.A.	N.A.	N.A. vs. N.A. ($p = 0.32$)
Wijn et al., 2018	NSCLC (127)	PD-1 inhibitor	Trivalent inactivated influenza vaccine	33%	26 vs. 22 (OR 1.20)	7 vs. 4 (OR 2.04)	N.A.
Läubli et al., 2018	NSCLC (16), RCC (4), melanoma (3)	PD-1 inhibitors	Trivalent inactivated influenza vaccine	100%	52.2*	26.1*	73.5*
Schenk, 2017	Melanoma (71), NSCLC (23), other (14)	PD-1 inhibitors	Influenza and/or pneumococcal vaccines	27.8%	N.A. vs. N.A. ($p = 0.265$)	N.A.	N.A.
Chong et al., 2019	NSCLC (170), melanoma (70), other (130)	PD(L)-1 and or CTLA-4 inhibitors	Trivalent or quadrivalent inactivated influenza vaccine	100%	20*	8*	N.A.

Legend: N.R. not reached; N.A. not available; NSCLC, non small cell lung cancer; RCC, renal cell carcinoma; OS, overall survival; ICIs, immune checkpoint inhibitors.
* included only vaccinated patients.

vaccine, Läubli et al. reported an unusual increase in irAEs (52.2%) and severe irAEs (26.1%). This study included two cases of encephalitis and a single case of autoimmune peripheral neuropathy (Läubli et al., 2018), raising important concerns about the safety of applying the seasonal influenza vaccination to patients undergoing immunotherapy. In contrast, three different studies, evaluating the safety of influenza vaccination in patients with solid tumors receiving ICIs, did not confirm these findings with a rate of irAEs comparable to published trials (Schenk, 2017) (Wijn et al., 2018) (Chong et al., 2019) [Table 4] and no correlation was reported in a recent study evaluating 101 patients who had developed immune-related myocarditis (Awadalla et al., 2019).

Concurrent administration of influenza vaccination with PD-1 or PD-L1 inhibitors therefore still remains the currently accepted community practice, based on the rationale that patients receiving immune checkpoint inhibitors may be at increased risk of infections due to their underlying malignancy. Therefore patients should receive appropriate vaccines to avoid infectious complications or delay in therapy (Rieger et al., 2018). To date limited data is available on the concomitant use of CTLA-4 inhibitors and influenza vaccine. Clinical experience suggests that patients on a CTLA-4 inhibitor (such as ipilimumab) are advised to wait 6–8 weeks after the last dose as ipilimumab generally exhibits a worse adverse effect profile than that of PD-1 or PD-L1 inhibitors (Rieger et al., 2018) (Chung, 2018).

Future prospective studies are warranted to better understanding the impact of anti-viral vaccines in patients treated with ICIs.

6. Conclusions and future perspectives

Immune checkpoint inhibitors are a new class of anticancer agents with a unique mechanism of action and a peculiar spectrum of side effects. In a relatively small fraction of unselected patients use of these agents lead to long-term disease control, with a more favorable safety profile than that seen with conventional anticancer agents, such as chemotherapy (Corrales et al., 2018; Rolfo et al., 2017). The potential for long-term exposure to these agents and their unique mechanisms of action, as well as the growing number of patients treated worldwide pose novel therapeutic challenges in clinical practice. Several retrospective studies have therefore evaluated the potential effects on therapeutic efficacy and/or safety of different concomitant medication that might theoretically interfere with the mechanisms of ICI action.

The role of antibiotics use in cancer patients treated with ICIs is one of the most well studied. Accumulating evidence indicates that the composition of the intestinal microflora has a major impact on patient prognosis, revealing a strong interaction between specific immunogenic bacteria and systemic immune response (Derosa et al., 2018b). Collectively, these studies suggest that ATB use seems to have a negative impact on outcomes in patients receiving ICIs by decreasing the diversity of gut microbiota and eliminating the most immunogenic bacteria (Derosa et al., 2018a). However, several questions still remain unanswered, including the optimal duration and window of antibiotic use respective to ICIs, the class and the route of administration of antibiotics, and the potential impact of other concomitant medications that might contribute to the dysbiosis of cancer patients, such as proton pump inhibitors, corticosteroids, and diet composition. In addition, the survival impact of antibiotics might be influenced in these studies by other poor prognostic factors that may be associated with the use of these medications, such as a poor ECOG PS, hospitalization, and concomitant presence of bacterial infections. Further prospective studies are needed to better clarify the impact of ATBs on the efficacy of ICIs and, in absence of clear evidence, the use of ATBs, especially for long or repeated courses, during immunotherapy should be carefully evaluated, bearing in mind that their use cannot be avoided or delayed in cases of bacterial infections and opportunistic infections present in patients requiring prolonged corticosteroid therapies due to severe irAEs.

The same considerations for ATBs are also valid for the concomitant use of proton pump inhibitors. Widely used PPIs might potentially

induce changes in gut microbioma and has been recently proposed to interfere with therapeutic efficacy of ICIs. If confirmed, this data may provide useful information for exploiting gut microbioma as a driver of antitumor immunity instead of only a predictive biomarker of efficacy for ICIs, allowing for overcoming primary resistance to these agents.

Moreover, an adequate evaluation of concomitant medications during ICIs is essential as several medications can affect not only immunotherapy efficacy, but also its safety profile. For instance, the use of PPIs and/or non-steroidal anti-inflammatory drugs (NSAIDs) has recently been advocated as one of the potential causes of acute tubulointerstitial nephritis (ATIN), a rare complication during anti-PD1 treatment. This rare drug-related renal manifestation is associated with drug-specific T-cells. ATIN may be exacerbated by the reactivation of the T-lymphocyte immune response following ICI therapy disrupting long-standing immunological tolerance to drugs that have been used safely previously, leading to the development of drug-induced ATIN (Koda et al., 2018) (Shirali et al., 2016). Although corticosteroid therapy is recommended, the recognition and discontinuation of concomitant drugs, especially those known to induce ATIN, is necessary for the management of kidney injury associated with anti-PD-1 therapy and may allow for reinitiating ICI therapy after complete resolution of renal damage and withdrawn of other potentially offending agents.

The use of corticosteroid is the mainstay treatment for irAEs, due to their immunosuppressive properties and in the hypothesis that this action could reduce the efficacy of immunotherapy. All ICI pivotal trials excluded patients requiring concomitant treatment with prednisone doses above 10 mg daily or equivalent. However, in clinical practice a not negligible portion of cancer patient needs corticosteroid doses of $\geq$10 mg a day for different clinical conditions, such as brain metastases and COPD control. Therefore, several retrospective studies evaluated the effect of early corticosteroid use in cancer patients treated with ICIs in real world populations. Collectively, these studies suggest that early corticosteroid use is associated with a poor prognosis, even though it was also correlated in some of these studies with other unfavorable prognostic factors, such as high tumor burden, poor ECOG PS, and brain metastases. Therefore in most of these studies multivariate analyses were conducted to minimize the confounding effect of these well-known prognostic factors (Arbour et al., 2018) (Scott and Pennell, 2018) (Fucà et al., 2019). Whether early corticosteroid use is truly an independent prognostic factor is still debated (Ricciuti et al., 2019) and it is still unclear whether the duration of treatment (prolonged versus intermittent use), the dosage and the route of administration might have a differential impact. Recently, multiple randomized phase III trial have evaluated multiple chemo-immunotherapy combinations in advanced NSCLC (Russo et al., 2018) and the use of corticosteroids as premedication in these trials seemed not to compromise the efficacy of ICIs addition (Gandhi et al., 2018) (Paz-Ares et al., 2018) (Socinski et al., 2018), suggesting that a prolonged instead of an intermittent use of corticosteroids might have a higher impact. In addition, the use of corticosteroids in patients experiencing irAES was reported not to negatively impact the outcomes of patients treated with either CTLA4 (Horvat et al., 2015) or PD(L)-1 inhibitors (von Pawel et al., 2017) (Leighl et al., 2015). Further prospective studies are needed to clearly define the role of concomitant use of corticosteroids at dosages above 10 mg/daily of prednisone.

Finally, the potential effect of vaccination in cancer patients treated with immunotherapy has been recently evaluated. The picture emerging from these studies is that the use of inactivated influenza vaccine in patients undergoing treatment with PD(L)-1 inhibitors is safe. Very limited data has been reported to date for other commonly used vaccines and their usage should be carefully evaluated in these patients.

In conclusion, multiple studies have evaluated the effects of different concomitant medications commonly used in clinical practice on ICI activity and/or safety. Prolonged corticosteroid therapies as well as extensive use of antibiotics, whenever possible, should be limited, given the potential negative impact on outcomes of such patients. However, the use of these agents in case of irAEs as well as other common indications (i.e. bacterial infections and COPD) should not be avoided and further prospective studies are needed. Moreover, the growing role of gut microbioma on the efficacy of ICIs deserves further investigations, not only as a marker of primary resistance to these agents, but also as a potential therapeutic strategy. Accumulating evidence suggest that inactivated influenza vaccine can be safely administrated to cancer patients in treatment with PD(L)-1 inhibitors, albeit the safety of other commonly used vaccine is far less known and deserves further studies. An accurate evaluation of concomitant medications is essential in patients receiving anticancer therapies, including ICIs, in order to prevent unexpected toxicities or compromise therapeutic efficacy.

Declaration of Competing Interest

No potential conflicts of interest declared.

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