Clinical Rheumatology (2019) 38:1513–1519
https://doi.org/10.1007/s10067-019-04451-2

BRIEF REPORT

Hydroxychloroquine is a safe and effective steroid-sparing agent for immune checkpoint inhibitor–induced inflammatory arthritis

Janet Roberts[1] · Michael Smylie[2] · John Walker[2] · Naveen S. Basappa[2] · Quincy Chu[2] · Michael Kolinsky[2] · Christopher Lyddell[3] · Carrie Ye[3]

Received: 31 October 2018 / Revised: 20 January 2019 / Accepted: 22 January 2019 / Published online: 30 January 2019

Abstract

Immunotherapy for cancer treatment continues to evolve, and immune checkpoints have proven successful therapeutic targets. With success has come the challenge of managing the commonly associated immune-related toxicities. Arthralgias and arthritis are a common immune-related adverse event (IrAE), well described in the literature (Pardoll Nat Rev Cancer 12:252–264, 2012; Diesendruck and Benhar Drug Resist Updat 30:39–47, 2017; Cappelli et al. Arthritis Care Res 69:1751–1763, 2017; Brahmer et al. J Clin Oncol 36:1714–1768, 2018; Smith and Bass (2017). The optimal management of immune checkpoint inhibitor (ICI)–induced arthritis remains unclear. We describe the first series using hydroxychloroquine as a first-line disease-modifying antirheumatic drug (DMARD) for patients without pre-existing autoimmune disease, who developed arthritis secondary to ICI's. This was a single-center retrospective observational study reporting all patients evaluated by rheumatologists affiliated with the University of Alberta, a large tertiary health care center in Northern Alberta, Canada, deemed to have inflammatory arthritis (IA) following ICIs. We identified 11 patients, without pre-existing autoimmune disease, who developed IA following ICIs. Most patients presented with a symmetrical polyarthritis with both large and small joint involvement. All patients were treated according to the outlined treatment protocol with hydroxychloroquine as a first-line steroid-sparing agent: either as monotherapy or in combination with tapering doses of systemic corticosteroids (3) or intra-articular steroid injections (6). One patient required the addition of methotrexate to control symptoms and none required biologic therapy. There were no reported adverse effects from hydroxychloroquine. Inflammatory arthritis is an important complication of ICIs leading to significant impact on patient quality of life. In our experience, in patients without pre-existing autoimmune disease, hydroxychloroquine is an effective first-line therapy for IA secondary to ICI therapy.

Keywords Autoimmune disease · Hydroxychloroquine · Immunotherapy · Inflammation · Neoplasms

Introduction

The last decade has seen a rapid increase in the use of immunotherapies in cancer treatment, and immune checkpoints have proven to be successful therapeutic targets. Immune checkpoints are inhibitory pathways which modulate the immune response, and in health, serve to minimize damage to healthy tissue, and prevent autoimmunity [1]. In the setting of malignancy, tumor cells use immune checkpoints to their advantage, as a mechanism to evade the endogenous antitumor immune response [2]. Hence, therapeutic targets blocking these pathways release the brakes on pivotal immune system inhibitory mechanisms, with the goal of eliciting a robust antitumor response, but at the risk of concomitantly inducing a host of immune-related adverse events (IrAEs).

✉ Janet Roberts
roberts5@ualberta.ca

[1] Division of Rheumatology, Department of Medicine, Dalhousie University, Suite 245 Nova Scotia Rehabilitation Building, 1341 Summer Street, Halifax, NS B3H 4K4, Canada

[2] Division of Medical Oncology, Department of Oncology, Cross Cancer Institute, University of Alberta, 11560 University Avenue, Edmonton, Alberta T6G 1Z2, Canada

[3] Division of Rheumatology, Department of Medicine, University of Alberta, 8-120 Clinical Sciences Building, 8440 112 St NW, Edmonton, AB T6G 2G3, Canada

The first immune checkpoint inhibitor (ICI) developed for therapeutic use was ipilimumab, a monoclonal antibody targeting cytotoxic T lymphocyte–associated protein (CTLA-4), approved by the FDA in 2011 for the treatment of metastatic melanoma. This was followed in short succession by agents targeting the programmed cell death 1 protein (PD-1), pembrolizumab and nivolumab, and those targeting the programmed cell death-ligand 1(PD-L1), atezolizumab, durvalumab, and avelumab. The list of approved indications for these drugs continues to expand and now spans multiple different tumor groups.

With increased use, there is increasing recognition of the unique adverse event profile associated with this class of medications and a recent systematic review revealed the wide range of presentations and severity of rheumatologic-specific IrAEs [3]. The most common of these is arthralgias and arthritis with many case series describing the development of an apparent immune-mediated inflammatory arthritis (IA). However, there is no consensus on the best treatment for these patients, with most published cases using escalating therapy with prednisone, methotrexate, and tumor necrosis factor inhibitors (TNFi), consistent with recently published guidelines [4].

We report a series of 11 patients evaluated at one Canadian academic center who developed IA during the course of immunotherapy. All patients followed a treatment algorithm that used hydroxychloroquine as the first-line steroid-sparing agent.

Materials and methods

Patients 18 years of age or older treated with either a CTLA-4 inhibitor and/or a PD-1/PD-L1 inhibitor for an advanced malignancy who were deemed to have IA following ICI therapy by their treating oncologist, and confirmed by a rheumatologist, were identified and included in this review. Patients must have had either clinical or ultrasound evidence of synovitis to be included. Patients with pre-existing autoimmune diseases were excluded. All patients followed a pre-set treatment algorithm that included hydroxychloroquine as a first-line steroid-sparing agent, with addition of methotrexate, then TNFi as required (Tables 1 and 2). Ethics approval through the University of Alberta was secured prior to the collection of patient data and the preparation of this manuscript. A retrospective review of each patient's electronic medical record was conducted and information including demographics, past medical history, malignancy type and stage, ICI history including date of initiation and discontinuation, both general IrAEs and rheumatologic-specific IrAEs, relevant serology, treatment, and outcomes were collected.

Results

Eleven patients who developed IA following ICI therapy between January 2016 and June 2018 were identified (Table 3). The mean age of patients was 65 years (range 43–82 years) and 55% were male. The cancer types treated included metastatic melanoma (3), small (1) and non–small cell lung cancer (4), transitional cell carcinoma of the bladder (1), squamous cell carcinoma of the anus (1), and prostate cancer (1). Nine patients were on ICI therapy at the time of arthritis onset, which included monotherapy pembrolizumab (5) or nivolumab (1), or combination therapy with durvalumab/tremelimumab (2) or pembrolizumab and docetaxel (1). In one case, combination therapy with ipilimumab and nivolumab was subsequently switched to monotherapy pembrolizumab after development of autoimmune hepatitis.

Mean time to onset of joint symptoms after initiation of immunotherapy was 26 weeks (range 3–142). In two patients, the onset of arthritis occurred at 9 weeks and 48 weeks after stopping the ICI for other IrAEs. One patient was positive for rheumatoid factor (RF) pre-ICI with no history of pre-existing arthritis. The remainder were negative for RF and anti-cyclic citrullinated protein (anti-CCP). The pattern of joint involvement included symmetrical large and small joint polyarthritis (6), asymmetrical oligoarthritis (3), polymyalgia rheumatica (PMR)–onset polyarthritis (1) and monoarthritis (1). Seven patients experienced other IrAEs including hepatitis, hypothyroidism, rash, acute interstitial nephritis (AIN), neuropathy, sicca, and duodenitis.

In three cases, corticosteroids were used to treat the arthritis, and in two additional cases, patients were on a tapering dose of prednisone for other IrAEs (duodenitis and AIN) when the arthritis began. In two of these cases, there was a delay in referral to rheumatology and patients were treated with high doses of prednisone (50–80 mg/day with taper) prescribed by their oncologist. In the other case, the treating rheumatologist used a much smaller dose of 10 mg of prednisone daily. The average pre-hydroxychloroquine prednisone dose in the three patients in whom prednisone was used to specifically treat the IA was 1548 mg (range of 770–2700 mg), while the average post-hydroxychloroquine dose was 260 (range of 0–630 mg). All patients treated with systemic corticosteroids were able to taper off without flare of their IA on hydroxychloroquine monotherapy. Six patients were treated with intra-articular steroids at presentation to rheumatology.

All patients were treated with hydroxychloroquine at a dose of 200-400 mg/day (based on weight). One patient passed away of a bleeding gastric ulcer 1 month after starting hydroxychloroquine, and thus, response could not be assessed. Of the remaining ten patients, seven achieved full response with complete resolution of their joint swelling and pain. Three patients had improvement of their IA symptoms,

Table 1 Overview of the management of ICI-associated inflammatory arthritis

Type of IA	CTCAE grade	ICI management	IA management
Monoarthritis	1	Continue	1) NSAID trial for 4 weeks 2) If 1) inadequate, iaGC[a] 3) If 2) inadequate, start SSA[b]
	2 or 3	Consider holding	1) iaGC[a] 2) If iaGC inadequate, start SSA[b]
Oligoarthritis Polyarthritis	1	Continue	1) Start SSA[b]; iaGC[a] as indicated[c]
	2	Consider holding	1) Start SSA[b]; iaGC[a] as indicated[c] 2) If 1) inadequate, add prednisone 10–20 mg po daily, with taper over 6–8 weeks
	3	Hold	1) Prednisone 10–20 mg po daily, with taper over 6–8 weeks; start SSA[b]; iaGC[a] as indicated[c] 2) If 1) inadequate, prednisone 20 mg–1 mg/kg po daily tapering to 20 mg within 2–4 weeks

IA inflammatory arthritis, *CTCAE* Common Terminology Criteria for Adverse Events, *ICI* immune checkpoint inhibitor, *NSAID* non-steroidal anti-inflammatory, *iaGC* intra-articular glucocorticoid, *SSA* steroid-sparing agent

[a] Depomedrol 20–80 mg depending on the joint, can be repeated up to every 3 months

[b] See Table 2: stepwise approach to steroid-sparing agent

[c] iaGC generally used for medium to large joints that are particularly affecting patient's function

but not complete resolution. Of these three patients, one required addition of methotrexate and the other two felt their IA symptoms were tolerable and did not want to escalate therapy. No patients required escalation of therapy to include a biologic.

The duration of follow-up in these patients ranges from 2 to 20 months. Response to hydroxychloroquine generally occurred within 2 months. In one patient who developed PMR-onset inflammatory polyarthritis of the wrists, MCP, and PIP joints with synovitis on examination and confirmed by musculoskeletal ultrasound, significant clinical and sonographic improvement was documented after just 1 month of treatment with hydroxychloroquine without any corticosteroid use, even with ongoing ICI therapy (Fig. 1). No serious adverse effects from hydroxychloroquine were seen in these patients.

None of the patients had their ICI permanently discontinued due to their IA. Four patients continued ICI therapy without worsening of their IA, five patients had their ICI therapy discontinued due to other IrAEs, and two patients had their ICI stopped due to tumor progression. With respect to tumor response, seven had a full or partial response to ICI and four had disease progression with one death.

Discussion

While the majority of IrAEs resolve with a short course of corticosteroids and discontinuation of immunotherapy, arthritis can be more persistent and require treatment even after immunotherapy cessation [5]. Very little is known about the role of steroid-sparing agents in these patients. Case series

Table 2 Stepwise approach to steroid-sparing agent

Step	Steroid-sparing agent	Notes
1	Hydroxychloroquine 5 mg/kg po daily	• Patients should get baseline and annual eye exam to screen for retinotoxicity
2	Methotrexate 15–25 mg po or subcutaneous weekly	• If no response to hydroxychloroquine, switch to methotrexate • If partial, but inadequate response to hydroxychloroquine, add on methotrexate • Before initiation of methotrexate, patients need hepatitis B and C screening and baseline CXR; patients need monthly CBCd, AST, ALT, albumin, Cr monitoring
3	Consider additional SSA such as sulfasalazine, leflunomide, or TNFi	• Dependent on access to TNFi • If no response to methotrexate, switch to another SSA • If partial, but inadequate response to methotrexate, add on additional SSA • Before initiation of these drugs, patients need hepatitis B and C screening and baseline CXR • For sulfasalazine and leflunomide, patients need monthly CBCd, AST, ALT, albumin, Cr monitoring • Prior to initiation of TNFi, patients need to be screened for latent and active TB with TBST and CXR

CXR chest X-ray, *CBCd* complete cell count with differential, *AST* aspartate aminotransferase, *ALT* alanine transaminase, *Cr* creatinine, *TNFi* tumor necrosis factor inhibitor, *TB* tuberculosis, *TBST* tuberculin skin test

Table 3 Patient demographics, malignancy type and response, immunotherapy, rheumatological treatment and response

Age/sex	Malignancy	ICI	Pattern of arthritis	Treatment	Treatment response	Tumor response	ICI status	CTCAE grade
43/M	Melanoma	Nivolumab/Ipilimumab (5 weeks)[a] Pembrolizumab (3 weeks)	Oligoarthritis	HCQ IaGC knees, ankles, L SIJ	Partial	No progression	Course completed	2
60/F	NSCLC	Pembrolizumab (142 weeks)	Polyarthritis	HCQ IaGC knee	Full	No progression	Stopped due to digital ischemia	1
77/M	TCC bladder	Durvalumab/tremelimumab (12 weeks)	Polyarthritis	Prednisone[b] HCQ	Unknown	Progression (deceased)	Stopped due to arthritis and delirium	3
82/M	NSCLC	Pembrolizumab (9 weeks)	Polyarthritis	Prednisone[c] HCQ	Full	No progression	Temporarily held due to arthritis	2
78/F	NSCLC	Pembrolizumab (16 weeks)	Polyarthritis	HCQ	Full	No progression	Treatment ongoing	2
54/F	Melanoma	Nivolumab/ipilimumab (12 weeks) Nivolumab (4 weeks)	Polyarthritis	Prednisone[d] HCQ IaGC knees	Full	No progression	Stopped due to acute interstitial nephritis	1
73/M	Prostate	Pembrolizumab (16 weeks)	Oligoarthritis	HCQ	Partial	Progression	Stopped due to progression	2
80/M	SCC lung	Pembrolizumab (12 weeks)	Polyarthritis	HCQ	Full	Progression	Held due to acute colitis	2
67/M	Melanoma	Clinical Trial: Ipilimumab/nivolumab or combination (12 weeks)	Monoarthritis (knee)	Prednisone[e] HCQ IaGC (knee)	Full	No Progression	Stopped due to duodenitis	1
57/F	SCLC	Nivolumab (24 weeks)	Polyarthritis	Prednisone[f] HCQ MTX IaGC wrists	Partial required addition of MTX	Progression	Stopped due to progression	2
50/F[g]	SCC anus	Durvalumab/tremelimumab (3 weeks)	Oligoarthritis	HCQ IaGC ankle	Full	No progression	Treatment ongoing	1

M male, *F* female, *HCQ* hydroxychloroquine, *IaGC* intra-articular glucocorticoid injection, *MTX* methotrexate, *SIJ* sacroiliac joint, *CTCAE* common terminology criteria for adverse events

[a] Combination therapy discontinued due to hepatitis

[b] Pre-HCQ cumulative prednisone dose of 2700 mg, post-HCQ cumulative prednisone dose 630

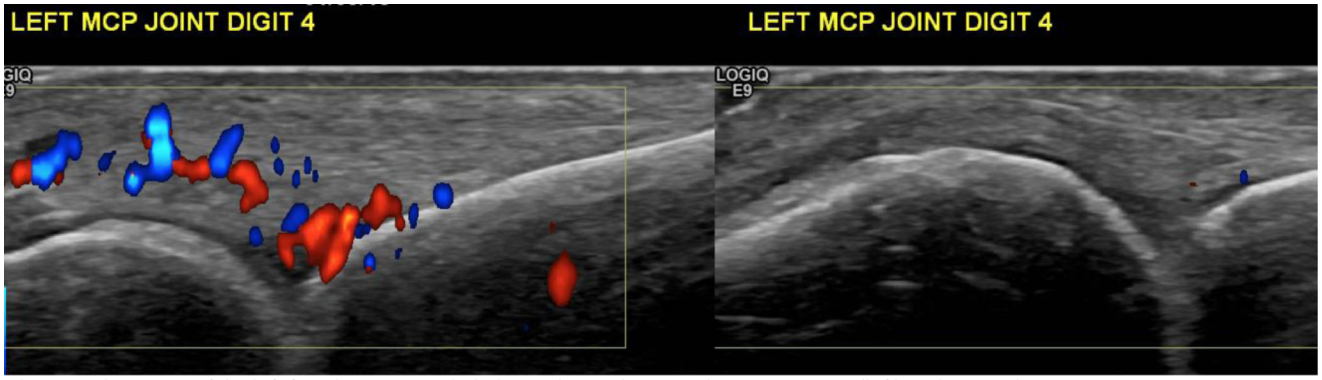
[c] Pre-HCQ cumulative prednisone dose of 1175 mg, post-HCQ cumulative prednisone dose 0 mg

[d] Arthritis developed 1 year after stopping ICI due to acute interstitial nephritis (AIN), while patient on prednisone taper of 5 mg daily for AIN

[e] Arthritis developed 3 months after stopping ICI due to duodenitis, while patient on prednisone taper of 10 mg daily

[f] Pre-HCQ cumulative prednisone dose of 770 mg, post-HCQ cumulative prednisone dose of 150 mg

[g] Positive rheumatoid factor pre-ICI



Ultrasound imaging of the left fourth metacarpal phalangeal joint (patient 9) pre treatment (left) and 1 month post hydroxychloroquine initiation (right).
(Left) Power Doppler ultrasound showing enhancement of synovitis
(Right) No increased Power Doppler signal one month after starting hydroxychloroquine

Fig. 1 Ultrasound imaging of the left fourth metacarpal phalangeal joint (patient 9) pre-treatment (left) and 1 month post hydroxychloroquine initiation (right). Power Doppler ultrasound showing enhancement of synovitis (left). No increased Power Doppler signal 1 month after starting hydroxychloroquine (right)

have described the use of DMARDs including methotrexate and biologics including TNFi and most recently tocilizumab [6, 7]. The Society for Immunotherapy of Cancer (SITC) recommendations for treatment of IA due to ICI therapy include methotrexate, leflunomide, sulfasalazine, and TNFi, but do not mention hydroxychloroquine as a potential steroid-sparing agent [8]. Similarly, the American Society of Clinical Oncology (ASCO) clinical practice guidelines for the treatment of IrAEs do not include Plaquenil in their list of synthetic DMARDs [4]. To date, there have only been two published cases in which hydroxychloroquine has been used as a steroid-sparing agent [9, 10].

Hydroxychloroquine is an immune-modulating drug which inhibits the production of inflammatory cytokines via multiple mechanisms including inhibition of innate immune system activation through its effects on toll-like receptors [11]. While originally developed as an antimalarial, it has since been shown to have far reaching therapeutic properties including anti-inflammatory, anti-infective, anti-thrombotic, and metabolic effects [12]. Its use in SLE and rheumatoid arthritis is well established with a favorable safety profile [13, 14]. Hydroxychloroquine use in cancer therapy is also being increasingly explored for its direct effect on cancer cells through induction of apoptosis and inhibition of autophagy and its synergistic effect with conventional chemotherapeutic agents [15, 16].

When faced with patients with arthritis induced by ICI inhibition, the rheumatologist has limited data to guide treatment decisions. Recently, international clinical practice guidelines on the management of IrAEs have been published by the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) both of which recommend corticosteroids as the initial treatment for grade 2 IA that persists despite analgesics, and for grade 3 or 4 IA, along with referral to rheumatology [4, 17]. However, there is a caveat in that the ASCO guidelines state that, while corticosteroids can be used as part of initial therapy in inflammatory arthritis, due to likely prolonged treatment requirements, physicians should consider starting corticosteroid-sparing agents earlier than one would with other IrAEs. Short-term corticosteroid treatment is generally considered safe and has not been associated with an attenuated antitumor response [18]. In fact, overall, it appears that patients who experience rheumatic IrAEs have a higher antitumor response compared to those without any IrAE [19]. The dilemma occurs when patients are unable to taper corticosteroids without return of symptoms. It is often at this stage that referral to rheumatology occurs. The effect of disease modifying agents and biologics on the antitumor response is poorly understood. While TNFi are generally considered safe in the short term and are commonly used in the treatment of ICI-induced colitis, a recent case report described loss of tumor response after use of an IL-17 inhibitor [20]. The effect of methotrexate on tumor response is largely unknown, but there is theoretical concern of any immunosuppression interfering with ICI therapy.

We describe 11 patients with ICI-induced arthritis who were treated with hydroxychloroquine monotherapy or with tapering concomitant oral or intra-articular corticosteroids. While treatment to a target of low disease activity or remission is the gold standard in rheumatoid arthritis, it is currently unknown what the "target" for treatment is in this unique patient population. Although not all patients achieved full resolution of their IA symptoms, there is no consensus on what the goal of IA therapy should be. One potential treatment target is clinical resolution or improvement allowing continued ICI therapy if indicated. Nine of our 11 patients were able to achieve this target with hydroxychloroquine without on-going corticosteroid use. It is important to note that none of the patients in this series had pre-existing IA prior to ICI initiation, as these

patients may require stronger conventional immunomodulators such as methotrexate or biologics.

Increased and earlier recognition of IA in the oncology community with early referral to rheumatology may minimize corticosteroid use, or even avoid it altogether, and improve treatment outcomes. At our center, we have developed a close working relationship with oncology and these patients are generally seen within 1–2 weeks of referral, often before initiation of corticosteroids. In the majority of these patients, hydroxychloroquine was initiated prior to starting corticosteroids thus significantly limiting corticosteroid exposure, as many of them avoided prednisone use altogether despite grade 2 and above IA. In the three patients treated with prednisone, the average cumulative pre-hydroxychloroquine dose was significantly higher (1548 mg) than the post-hydroxychloroquine dose (260 mg), and in two cases, the high doses of prednisone required pre-hydroxychloroquine are likely a reflection of delay in referral to rheumatology. There were no documented side effects attributable to hydroxychloroquine in this small sample. This is consistent with the known tolerability and safety record of hydroxychloroquine in the rheumatoid arthritis and lupus literature [13, 14]. In summary, in these patients with early onset IA, hydroxychloroquine appears to be a safe and effective steroid-sparing agent for ICI-induced IA.

Compliance with ethical standards

Retrospective data were used, and patients were not contacted for this study. Thus, ethics approval was received but individual patient informed consent was not required for this study by our institution.

Disclosures None.

References

1. Pardoll DM (2012) The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 12:252–264
2. Diesendruck Y, Benhar I (2017) Novel immune check point inhibiting antibodies in cancer therapy – opportunities and challenges. Drug Resist Updat 30:39–47
3. Cappelli LC, Gutierrez AK, Bingham CO 3rd, Shah AA (2017) Rheumatic and musculoskeletal immune-related adverse events due to immune checkpoint inhibitors: a systematic review of the literature. Arthritis Care Res 69:1751–1763
4. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, Chau I, Ernstoff MS, Gardner JM, Ginex P, Hallmeyer S, Holter Chakrabarty J, Leighl NB, Mammen JS, McDermott DF, Naing A, Nastoupil LJ, Phillips T, Porter LD, Puzanov I, Reichner CA, Santomasso BD, Seigel C, Spira A, Suarez-Almazor ME, Wang Y, Weber JS, Wolchok JD, Thompson JA, in collaboration with the National Comprehensive Cancer Network (2018) Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline. J Clin Oncol 36:1714–1768
5. Smith MH, Bass AR (2017) Arthritis after cancer immunotherapy: symptom duration and treatment response. Arthritis Care Res. https://doi.org/10.1002/acr.23467
6. Cappelli LC, Gutierrez AK, Baer AN, Albayda J, Manno RL, Haque U, Lipson EJ, Bleich KB, Shah AA, Naidoo J, Brahmer JR, le D, Bingham CO III (2017) Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab. Ann Rheum Dis 76:43–50
7. Kim ST, Tayar J, Trinh V, Suarez-Almazor M, Garcia S et al (2017) Successful treatment of arthritis induced by checkpoint inhibitors with tocilizumab: a case series. Ann Rheum Dis 76:2061–2064
8. Puzanov I, Diab A, Abdallah K et al (2017) Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) toxicity management working group. J Immunother Cancer 5:95. https://doi.org/10.1186/s40425-017-0300-z
9. Calabrese C, Kirchner E, Kontzias K, Velcheti V, Calabrese LH (2017) Rheumatic immune-related adverse events of checkpoint therapy for cancer: case series of a new nosological entity. RMD Open 3:e000412. https://doi.org/10.1136/rmdopen-2016-000412
10. Belkhir R, Burel SL, Dunogeant L, Marabelle A, Hollebecque A, Besse B, Leary A, Voisin AL, Pontoizeau C, Coutte L, Pertuiset E, Mouterde G, Fain O, Lambotte O, Mariette X (2017) Rheumatoid arthritis and polymyalgia rheumatic occuring after immune checkpoint inhibitor treatment. Ann Rheum Dis 76:1747–1750
11. Kuznik A, Bencina M, Svajger U, Jeras M, Rozman B, Jerala R (2011) Mechanism of endosomal TLR inhibition by antimalarial drugs and imidazoquinolines. J Immunol 186:4794–4804. https://doi.org/10.4049/jimmunol.1000702
12. Platone D, Koudriavtseva T (2018) Current and future use of chlorquine and hydroxycloroquine in infectious, immune, neoplastic, and neurological diseases: a mini-review. Clin Drug Investig 38:653–671
13. Willis R, Seif AM, McGwin G Jr, Martinez-Martinez LA, González EB, Dang N, Papalardo E, Liu J, Vilá LM, Reveille JD, Alarcón GS, Pierangeli SS (2012) Effect of hydroxychloroquine treatment on pro-inflammatory cytokines and disease activity in SLE patients: data from LUMINA, a multiethnic US cohort. Lupus 21(8):830–835. https://doi.org/10.1177/0961203312437270
14. Suarez-Almazor ME, Belseck E, Shea B, Homik J, Wells G, Tugwell P (2000) Antimalarials for treating rheumatoid arthritis. Cochrane Database Syst Rev 2000(4):CD000959
15. Pascolo S (2016) Time to use a dose of chloroquine as an adjuvant to anti-cancer chemotherapies. Eur J Pharmacol 771:139–144
16. Verbaanderd C, Maes H, Schaaf MB, Sukhatme VP, Pantziarka P, Sukhatme V et al (2017) Repurposing drugs in oncology (ReDO)—chloroquine and hydroxychloroquine as anti-cancer agents. Ecancermedicalscience 11:1–35
17. Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, Jordan K, on behalf of the ESMO Guidelines Committee (2017) Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 28(Suppl_4):iv119–iv142
18. Horvat TZ, Adel NG, Dang TO, Momtaz P, Postow MA, Callahan MK et al (2015) Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center. J Clin Oncol 33:3193–3198
19. Kostine M, Rouxel L, Barnetche T, Veillon R, Martin F, Dutriaux C, Dousset L, Pham-Ledard A, Prey S, Beylot-Barry M, Daste A, Gross-Goupil M, Lallier J, Ravaud A, Forcade E, Bannwarth B, Truchetet ME, Richez C, Mehsen N, Schaeverbeke T, FHU ACRONIM (2018) Rheumatic disorders associated with immune

checkpoint inhibitors in patients with cancer – clinical aspects and relationship with tumour response: a single-centre prospective cohort study. Ann Rheum Dis 77:393–398

20. Esfahani K, Miller WH (2017) Reversal of autoimmune toxicity and loss of tumor response by interleukin-17 blockade. N Engl J Med 376:1989–1991