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High proportion of drug hypersensitivity reactions to sulfasalazine following its use in anti-PD-1 associated inflammatory arthritis

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Key messages:

Sulfasalazine use in anti-PD-1 associated inflammatory arthritis may be associated with more frequent hypersensitivity reactions

SIR, Checkpoint blockade has revolutionised the management of several cancers by targeting the coinhibitory pathways that down-modulate T cell receptor-mediated T cell activation. However the resulting enhanced T cell activation also gives rise to immune-related adverse events (IrAEs). Arthritis is an increasingly recognised IrAE following treatment with the licensed antibodies to programmed cell death protein-1 (PD-1) and may persist following discontinuation of anti-PD-1.[1]. [1] Treatment often consists of corticosteroids, with escalation if required to disease modifying anti-rheumatic drugs (DMARDs). However uncertainty exists about the possible impact of potent DMARD therapy on durability of cancer response with some oncologists reluctant to consider use of methotrexate.[2]

Sulfasalazine combines salicylic acid with the anti-microbial sulfapyridine and has been suggested as one possible therapy for IrAE.[1, 2] Sulfasalazine can cause a drug hypersensitivity reaction that rarely may be systemic and potentially life-threatening.[3] Importantly such drug hypersensitivity reactions are T cell mediated.[4, 5]

We reviewed all cases of anti-PD-1 associated inflammatory arthritis treated with sulfasalazine at our centre. Patient characteristics for the four patients are presented in Table 1. All had metastatic

melanoma treated with the anti-PD-1 antibody pembrolizumab and three had had prior checkpoint blockade with the anti-CTLA4 antibody ipilimumab.

In Case 1, the initial management of knee and then ankle monoarthritis was with intraarticular steroid but sulfasalazine was introduced after progression to involve both knees and ankles. Ten days later, he was admitted with pyrexia (37.7°C) and a widespread erythematous maculopapular rash. Blood tests revealed an acute rise in alanine transferase (66 U/L) and C-Reactive Protein (CRP) (189 mg/L) and new lymphopenia (0.8 $x10^9$/L). He improved with 3 days of intravenous methylprednisolone followed by a reducing course of oral prednisolone. Sulfasalazine and pembrolizumab were both discontinued.

In case 2, sulfasalazine was commenced for initial monoarthritis of the knee following only transient improvement with intra-articular steroid. Five days after starting sulfasalazine, he was admitted with fever (38.5°C) and cough with unremarkable chest radiograph and a raised CRP (78 mg/L). He was treated with antibiotics for a presumed infection of unknown origin (PUO). Sulfasalazine was suspended for one week and future pembrolizumab infusions were deferred. Eleven days after restarting sulfasalazine, he was readmitted with fevers and again treated for presumed PUO and sulfasalazine was stopped. A month later, sulfasalazine was restarted but nine days later he was admitted with low grade fever, non-productive cough, and raised CRP (170 mg/L). No source of infection was identified and he was treated with oral prednisolone and sulfasalazine was stopped. Five weeks later, an escalating dose of sulfasalazine was reintroduced, but on reduction in prednisolone he developed nausea, diarrhoea, deranged liver function tests (ALT 288 U/L) and raised CRP. Sulfasalazine was stopped and his symptoms resolved.

Case 3 had rash, facial swelling and fever but did not seek medical attention as her symptoms settled on stopping sulfasalazine.

Pembrolizumab was suspended in case 4 due to the development of a symmetrical polyarthritis involving the shoulders, knees and hands. Four months after the final pembrolizumab infusion, an escalating dose of sulfasalazine was introduced and five weeks later, he was admitted with a five day history of profound loose stool successfully treated with high dose steroids. Sulfasalazine was discontinued.

We observed a high proportion of adverse reactions with sulfasalazine in the context of anti-PD-1 associated inflammatory arthritis and sulfasalazine was discontinued in all cases. Drug hypersensitivity reactions are are mediated by drug-reactive T lymphocytes,[5] and the risk may increase with higher drug levels, or with alteration in T cell function, as exemplified by the association of amoxicillin-clavulanate hypersensitivity with the PTPN22 locus,[6] which encodes a regulator of T cell function. It is therefore plausible that inhibition of PD-1 might also increase risk and this might also apply to other drugs strongly associated with T cell mediated drug hypersensitivity syndromes such as carbamazapine and allopurinol.

In RA clinical trials the withdrawal rate for sulfasalazine was as high as 25%, but this was mostly due to the common side effects of nausea, headache and dizziness, with a drug rash occurring in only 4-5% and other hypersensitivity manifestations being much rarer.[3] Cutaneous and other IrAEs are common with checkpoint blockade, and could give rise to diagnostic uncertainty as illustrated in the second of our cases. However the temporal association, not observed in our experience with methotrexate, the high prevalence and similarity to the recognised sulfasalazine hypersensitivity syndrome, and the reoccurrence upon rechallenge, all point towards a genuine drug association. Our fourth case was different and characterised by colitis, but in this case pembrolizumab was discontinued four months before sulfasalazine was started. Colitis is a common IrAE following checkpoint blockade, and rare following sulfasalazine, suggesting this to be unrelated. However recent data indicate that the gut microbiome can influence emergence of IrAEs following checkpoint

blockade,[7] and since sulfasalazine has an antibiotic component, we cannot excludean indirect association through alteration of faecal flora.[8]

In conclusion we observed a high proportion of hypersensitivity reactions following use of sulfasalazine, and suggest caution in its use to manage anti-PD-1 related inflammatory arthritis.

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Conflicts of Interest

BAF has received consultancy fees from Novartis, Roche and BMS. AF has received consultancy fees from Novartis and Chugai.

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Table 1. Patient characteristics.

Case	Gender	Age	Previous immunotherapy	Cancer Response to anti-PD-1	Initial Joint presentation	Subsequent joint presentation	ANA	Months from Anti-PD1 to start of arthritis	Duration on sulfasalazine (days)	Reason for stopping SSZ	Management of Adverse event
1	Male	57	Ipilimumab. (Stopped due to hypophysitis and disease progression)	Stable	Monoarthritis	Symmetrical Oligoarthritis (knees and ankles)	Negative	4	10	fever, erythematous maculopapular rash across the face, neck, chest and back, acute rise in ALT and CRP and lymphopenia	Discontinuation IV and oral corticosteroid
2	Male	51	Ipilimumab. (Stopped due to hypophysitis and hepatitis)	Remission	Monoarthritis	Symmetrical Medium/large joint polyarthritis	Negative	7	a) 5 b) 11 c) 9 d) 21 (concomitant steroid)	a) fever, cough, raised CRP. b) fever, raised CRP. c) fever, non-productive cough, raised CRP. d) nausea, diarrhoea, raised ALT and CRP	a) Discontinuation b) Discontinuation c) Discontinuation and oral corticosteroid d) Discontinuation and oral corticosteroid
3	Female	50	Nil	Slight progression	Monoarthritis	Symmetrical Polyarthritis	1:400[1]	5	10	rash over chest, swelling around eyes and face, profound lethargy and fever.	Discontinuation
4	Male	77	Ipilimumab. (Stopped due to progression)	Remission	Symmetrical Polyarthritis	Symmetrical Polyarthritis	Negative	2	35	acute late onset colitis	Discontinuation IV and oral corticosteroid

Footnote: All cases were anti-CCP antibody and rheumatoid factor negative. ALT, alanine aminotransferase. CRP, C-reactive protein. [1]Predated introduction of sulfasalazine.