Clinical outcomes in cancer patients with immune checkpoint inhibitor-induced arthritis treated with methotrexate: a retrospective longitudinal monocentric pilot study

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Abstract

Objective

Immune-mediated adverse events (irAEs) from immune checkpoint inhibitors (ICIs) often require high-dose glucocorticoids (GCs), which can promote cancer progression and counteract ICI benefits. This study evaluated the articular and oncologic clinical outcomes of ICI-induced arthritis treated with methotrexate (MTX) as a GC-sparing agent.

Methods

Adult patients with ICI-induced arthritis in 2023 were included. Arthritis was assessed using the disease activity score on 28 joints by C-reactive protein (DAS28-CRP), with follow-ups every 3 months. All patients received subcutaneous MTX, and oncologic outcomes were evaluated using RECIST 1.1 criteria after one year.

Results

Fourteen patients (median age 74.5 years) with melanoma (64.3%), colorectal cancer (14.3%), lung cancer (14.3%), or Hodgkin's lymphoma (7.1%) were treated with PD1 antagonists (92.9%) or combined with CTLA4 blockers (7.1%). Arthritis presentations included oligo-arthritis (36%), mono-arthritis (29%), polyarthritis (21%), and polymyalgia rheumatica-like syndrome (14.3%), with a mean onset of 4.7±3.7 months post-ICI. MTX was started for all at a mean dose of 9.5±1.5 mg weekly, beginning at the first rheumatology visit in 78.5% of patients. Over a mean follow-up of 12.8±4.6 months, DAS28-CRP scores improved significantly, and prednisone dosage was in all reduced (3.6 mg at V4 vs. 8.4 mg at V0, p=0.003). No major MTX-related toxicities were noted. Cancer responses at follow-up were complete (50%), partial (21.4%), stable disease (7.1%), and progression (21.5%).

Conclusion

The use of MTX in ICI-induced arthritis showed promising results in reducing GC dosages and managing the inflammatory articular activity, with no major toxicities observed over one year. These findings suggest that MTX may be a viable GC-sparing option in this context, but larger, controlled studies are needed to confirm these observations and better understand the impact on both articular and oncologic outcomes.

Key words

immune checkpoint inhibitors, neoplasms, arthritis, methotrexate

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Introduction

Although immune checkpoint inhibitors (ICIs) have shown to be successful weapons against malignancies, they can induce potentially severe side effects called immune-related adverse events (irAEs), due to the activation of autoreactive T-cells (1). Among the rheumatic irAEs associated with the use of ICIs, arthritis has shown to occur in approximately 4% of recipients (2, 3). While around half of these patients respond to glucocorticoids (GCs) alone, up to 50% may require additional immunosuppressive agents to effectively manage the arthritis. Notably, inflammatory arthritis induced by ICIs tends to persist long-term and follows a chronic course, even after the cessation of immunotherapy (4, 5).

Accumulating evidence also suggests that high dosages of GCs used for treating irAEs due to treatment with ICIs may adversely affect tumour survival (6, 7). Therefore, introducing a disease-modifying anti-rheumatic drug (DMARD) for managing chronic rheumatic irAEs is crucial, both to control articular disease activity and to reduce GC dosage. However, a delicate balance must be maintained when administering immunosuppressive treatment to oncologic patients, as there are concerns about its potential impact on tumour progression, which may counteract the efficacy of ICIs (8).

For ICI-induced inflammatory arthritis (ICI-IA), the primary published observational reports have focused on conventional synthetic DMARDs (csDMARDs) such as methotrexate (MTX), sulfasalazine (SSZ), and hydroxychloroquine (HCQ), as well as on biological DMARDs (bDMARDs) including inhibitors of the tumour necrosis factor alpha (TNF-α-i) and interleukin-6 receptor (IL-6Ri) (9). MTX, in particular, has both anti-inflammatory and antiproliferative properties, which may help in managing inflammation while potentially offering oncologic positive results and safety (10, 11). A recent multicentre retrospective study comparing MTX, TNF-α-i, and IL-6Ri in the treatment of ICI-induced inflammatory arthritis revealed that MTX was associated with a significantly longer time to cancer progression compared to TNF-αi and IL-6Ri. However, it also demonstrated a slower time to arthritis control compared to the bDMARDs (12).

Considering the paucity of longitudinal follow-up data with standardised outcome measures of efficacy in terms of control of the ICI-IA and oncological safety, we aimed to evaluate the articular and oncologic outcomes of ICI-induced arthritis treated with MTX as a GC-sparing agent.

Methods

During 2023, all the adult patients (>18 years old) affected by a solid tumour and who developed ICI-IA after receiving regimens containing ICIs including inhibitors of programmed-death-1 protein (PD-1), programmed-death-ligand-1 protein (PDL1) and cytotoxic T-lymphocyte antigen 4 (CTLA4), were assessed in the Academic Division of Clinical Rheumatology, University of Genova, San Martino Polyclinic Hospital in Italy. These assessments were initiated upon rheumatological referral requested by oncologists from the Academic Division of Oncology at the same Polyclinic.

Individuals who exhibited symptoms and signs suggestive of arthritis, prompting clinical suspicion, were included in the assessment. During the initial rheumatologic visit, a thorough articular and general physical examination was performed (13, 14). In addition, we conducted a comprehensive laboratory assessment that included blood examinations to evaluate the full blood count, liver and kidney function, and inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and fibrinogen concentration. We also tested for rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA), antinuclear antibodies (ANA), and extractable nuclear antigens (ENA). Ultrasonography of the affected sites was performed and reported using the Outcome Measures in Rheumatology (OMERACT) scoring systems derived from rheumatoid arthritis (RA) (15, 16).

Articular disease activity was assessed by using a clinimetric score derived from rheumatoid arthritis (RA): the activity score on 28 joints by C-reactive protein

Table I. Cancer types, received immune checkpoint inhibitor and inflammatory rheumatic associated manifestations.

Cancer type	Number of patients	Received immune checkpoint inhibitor	Inflammatory rheumatic manifestation
Melanoma	9 (64.3%)	Nivolumab (5/9, 56%)	Polyarthritis (n=2), Oligo-arthritis (n=1), Mono-arthritis (n=1), PMR-like syndrome (n=1)
		Pembrolizumab (3/9, 33%)	Oligo-arthritis (n=2), PMR-like syndrome (n=1)
		Nivolumab and Ipilimumab (1/9, 11%)	Oligo-arthritis (n=1)
Colorectal cancer	2 (14.3%)	Pembrolizumab (2/2, 100%)	Polyarthritis (n=1), Mono-arthritis (n=1)
Non-small cell lung cancer	2 (14.3%)	Cemiplimab (1/2, 50%)	Oligo-arthritis (n=1)
		Nivolumab (1/2, 50%)	Mono-arthritis (n=1)
Hodgkin's lymphoma	1 (7.1%)	Nivolumab	Mono-arthritis (n=1)

(DAS28-CRP) (17). This composite score takes into account the patient's pain reported on a visual analogue scale (VAS, ranging from 0, indicating no pain, to 10, indicating extremely intense pain), along with the number of tender joints (NTJ) and the number of swollen joints (NSJ). The DAS28 cut-off of 2.6 defined remission (when lower values) or active disease (higher values) (18). Given that the DAS28 score has certain limitations and excludes some joints, such as those in the feet, from its calculation, we also evaluated the individual components (VAS, NTJ, and NSJ) as additional efficacy outcome measures during follow-up.

The patients were followed up every three months in accordance with a tight control approach (19). All patients were prescribed subcutaneous methotrexate (MTX) in combination with oral glucocorticoid (GC) treatment. Total body imaging was carried out using computed tomography (CT) during their follow-up, which included chest and abdomen scans for everyone. Additionally, patients with melanoma received brain scans. One patient with lymphoma had their follow-up imaging done with positron emission tomography (PET)/CT. The timing of the imaging follow-up was guided by clinical indications provided by the oncologist.

The Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 was used to describe the oncologic outcomes of the patients during treatment and follow-up (20).

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. All patients undergoing rheumatological visits at our Institution are routinely asked to provide a written informed consent for the retrospective utilisation of their anonymised clinical data for research purposes (CONSAZHQA_0001).

Statistical analysis

Categorical variables were compared using the chi-square (χ^2) test. To assess the normality of metric data before each statistical test, the Kolmogorov-Smirnov test and Q–Q plots were used. For normally distributed data, parametric tests such as the independent t-test for two samples or analysis of variance (ANOVA) for multiple samples were applied. For data that did not follow a normal distribution, non-parametric tests such as the Mann-Whitney or Kruskal-Wallis tests were used. Predictive analysis was conducted using demographic, clinical, laboratory, and imaging features at baseline as independent variables, with the number of assessments during active disease and the discontinuation of prednisone treatment at the first year as dependent variables. Initially, a univariate analysis was performed to identify significant associations between each independent variable and the outcomes. Multivariate analysis was conducted only for predictors with p-values <0.1 in the univariate analysis. Statistical significance was set at p-values <0.05. All statistical analyses were performed using Datatab®.

Results

Fourteen patients (male to female ratio = 1:1, mean age 71.1±11 years) were assessed. The oncologic diagnosis was melanoma in 64.3% (n=9), colorectal cancer in 14.3% (n=2), non-small cell lung cancer in 14.3% (n=2) and Hodgkin's lymphoma in 7.1% (n = 1) receiving anti-PD1 (nivolumab in 50%, pembrolizumab in 35.8% cemiplimab in 7.1%), and/or combination treatment with CTLA4 blockers (ipilimumab + nivolumab in 7.1%). Three patients (21.4%) received prior chemotherapy before treatment with immune checkpoint inhibitors: one patient with colorectal cancer received the XELOX scheme, one patient with non-small cell lung cancer received vinorelbine, and one patient with Hodgkin's lymphoma received the ABVD scheme.

Polyarthritis (4 or more joints inflamed) occurred in 3 patients (21.4%), oligo-arthritis (less than 4 joints inflamed) in 5 (35.7%), mono-arthritis in 4 (28.5%) and a polymyalgia rheumatica (PMR)-like syndrome with an inflammatory involvement of articular and peri-articular of the shoulder girdle in 2 (14.3%) after a mean onset time of 4.7±3.7 months from the starting of ICI (Table I). The mean follow-up duration was 12.8 ± 4.6 months (range 6–18).

Seven patients (50%) exhibited additional extra-articular irAEs alongside ICI-IA: two had gastrointestinal side effects with colitis necessitating high-dose prednisone (>50 mg daily), one patient was treated by the consultant dermatologist for extensive skin psoriasis with anti-interleukin-23 therapy (tildrakizumab) and also had sicca syndrome, one showed diffuse vitiligo, three patients experienced altered thyroid function (2 with hypothyroidism requiring levothyroxine replacement and the other with hyperthyroidism managed with tapazole), one patient presented

Table II. Clinical features of patients at first visit (V0).

Parameter	Mean ± SD (or range in brackets) and frequencies (%)
Number of tender joints	2.5 ± 1.9
Number of swollen joints	1.7 (range 0-8)
VAS	5.1 ± 1.7
DAS28(PCR)	3.8 ± 0.6
Prednisone dosage assumed by patients at V0	19.6 mg (range 0-75 mg)
Erythrocyte sedimentation rate	61.4 ± 22.3 mm/h
C-reactive protein	18.8 ± 11.3 mg/L
Positivity for rheumatoid factor	0 (0%)
Positivity for anti-citrullinated peptide autoantibodies	0 (0%)
Positivity for antinuclear antibodies (ANA)	6 (42.8%)
Positivity for antibodies against extractable nuclear antigens (ENA)	1 (6%): positivity for RNP without clinical symptoms of MCTD 1 (6%): positivity for SSA without clinical signs or symptoms of sicca syndrome
Pattern of antinuclear antibodies	1:160 speckled (3), 1:320 speckled (2, 1 of them with pattern DFS70 like) and 1:640 speckled (1)
Imaging findings on ultrasound:	
% of patients with synovitis	12 (85.7%)
% of patients with tenosynovitis	4 (28.5%)
% of patients with effusion	3 (21.4%)
% of patients with erosions	3 (21.4%)

with adrenal insufficiency, and one had significantly elevated plasma creatine-phosphokinase concentrations (>1500 U/ml) that responded to high-dose prednisone treatment without evidence of immune-mediated myopathy based on clinical, laboratory, and imaging evaluations. Among these seven patients, two had multiple extra-articular irAEs.

In six patients (43%), ICI treatment was continued during the onset of arthritis, while in 8 patients it was either discontinued or temporarily paused: four patients had cessation due to the emergence of extra-articular irAEs, one patient experienced temporary suspension due to ICI-induced arthritis, and one patient switched to a combination therapy of BRAF and MEK inhibitors (encorafenib and binimetinib) due to melanoma progression. The other patients ceased treatment because of stable disease (n=1) or achieving complete (n=2) or partial (n=1) oncologic responses. In

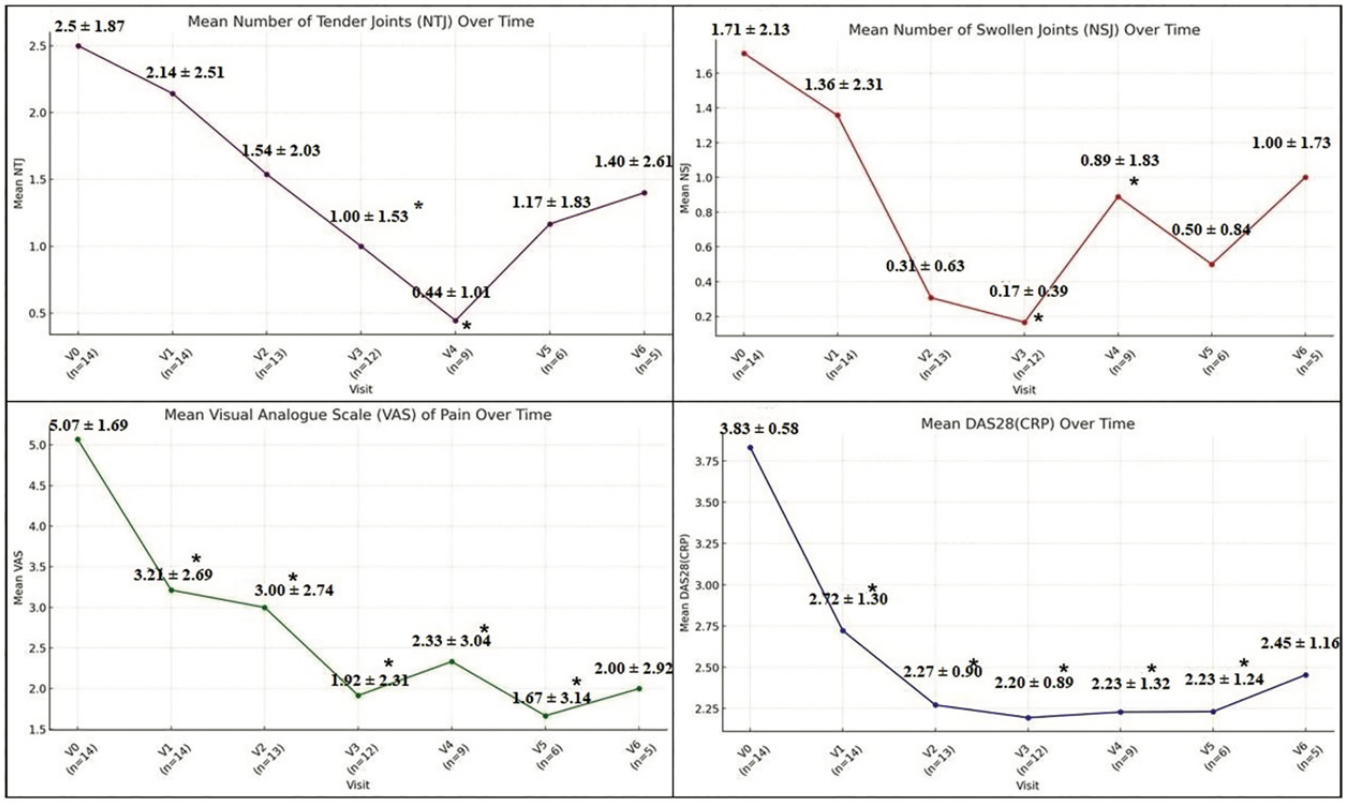

Fig. 1. Parameters of arthritis' disease activity during follow-up visits.
DAS28 refers to the Disease Activity Score-28. Values marked with * indicate a statistically significant difference compared to the baseline assessment at V0. Specifically:
- For NTJ (number of tender Joints), there was a significant reduction at V3 and V4 compared to V0 (p=0.034 and *p*=0.003, respectively).
- For NSJ (number of swollen joints), significant reductions were observed at V2 (*p*=0.032) and V3 (*p*=0.018) compared to V0.
- For VAS (visual analogue scale of pain), significant differences were noted at V1 (*p*=0.040), V2 (*p*=0.030), V3 (*p*=0.001), V4 (*p*=0.031), and V5 (*p*=0.045) compared to V0.
- For DAS28(CRP), significant differences were found at V1 (*p*=0.009), V2 (*p*<0.001), V3 (*p*<0.001), V4 (*p*=0.006), and V5 (*p*=0.024) compared to V0.

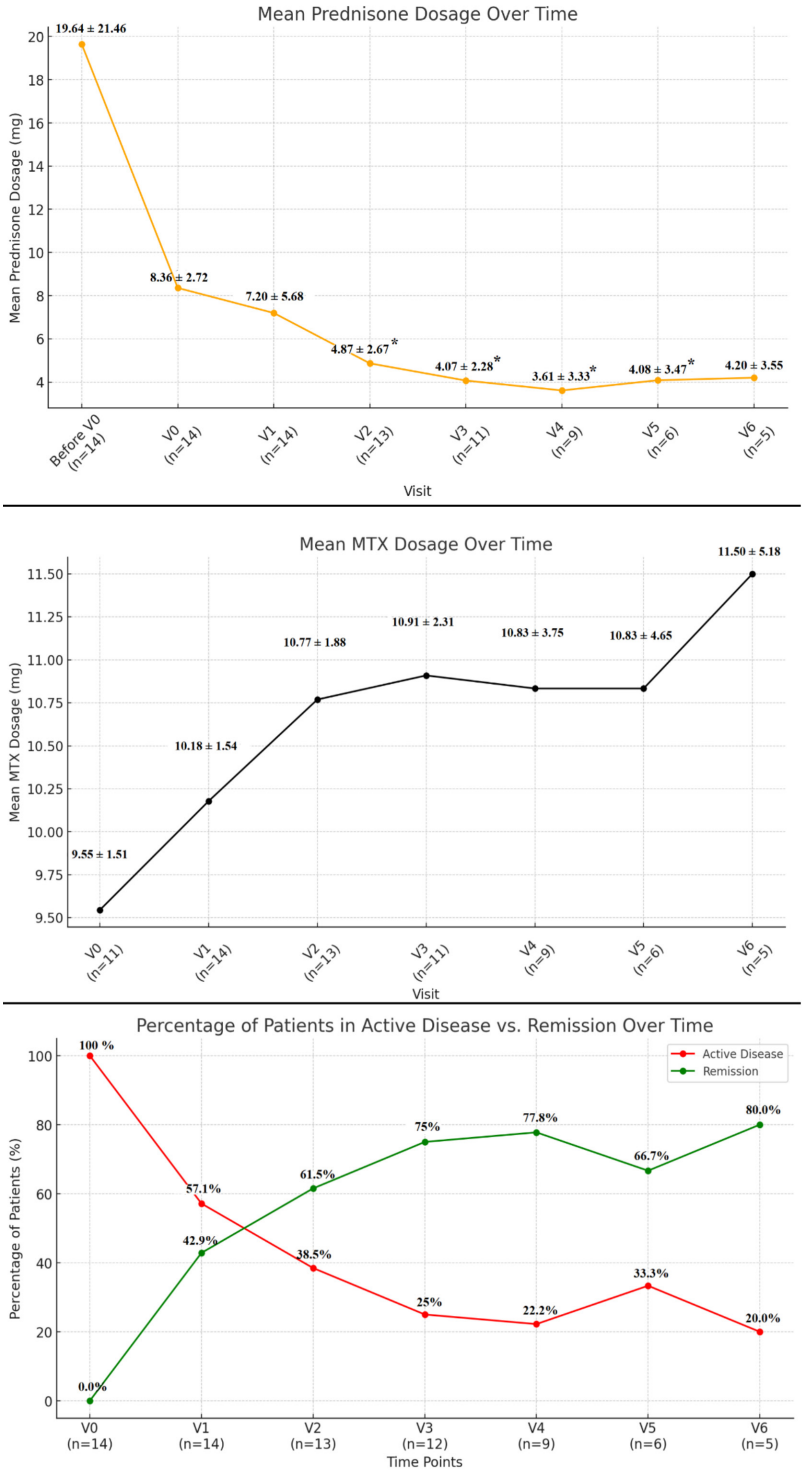

Fig. 2. Parameters related to treatment (prednisone and methotrexate dosage) and patients in remission *vs*. active disease at each assessment.
Values marked with * indicate a statistically significant difference compared to the baseline assessment at V0. Specifically: for prednisone dosage, there was a significant reduction at V2, V3, V4 and V5 compared to V0 (p=0.002, p<0.001, p=0.003 and p=0.028, respectively).

two patients the reasons of discontinuation were related both to extra-articular toxicities and tumour response.

The detailed clinical, laboratory and ultrasonographic features of patients at first visit (V0) are reported in Table II. MTX was prescribed in all patients with an initial mean dosage of 9.5±1.5 mg/weekly (Fig. 1); in 78.5% of patients (11/14) it was started at V0. All patients received folic acid 5 mg daily 24 hours after the assumption of weekly MTX.

DAS28-CRP values showed improvement over the course of the follow-up period (Fig. 1). There was a significant reduction in DAS28-CRP from baseline at V0 to V1-V5, along with decreases in the number of tender joints (NTJ), number of swollen joints (NSJ), and visual analogue scale (VAS) scores. Furthermore, patients significantly reduced their daily prednisone dosage, with notable reductions from V0 at V2, V3, V4, and V5. Remission rates also increased from V0 to V6 (Fig. 2).

No major toxicities related to MTX treatment were observed. One patient (7.1%) exhibited mild hypertransaminasaemia, with liver enzyme levels (aspartate and alanine transaminases) rising to less than 1.5 times the upper limit. In this case, MTX was transitorily interrupted for 2 weeks, and folic acid was assumed daily during this period and then restarted with the same dosage.

Follow-up imaging was conducted 9.5±5.9 months after the methotrexate (MTX) prescription, with data available for all but one patient (13/14, 93%). At follow-up, seven patients (50%) sustained a complete cancer response, three patients (21.4%) exhibited a partial response, and one patient (7.1%) had stable disease. However, three individuals (21.5%) showed cancer progression on CT scans: two had increased diameters of melanoma-related lymph-nodal metastases. One of these two melanoma patients required a change in treatment from combination therapy with ipilimumab and nivolumab to encorafenib and binimetinib, resulting in a partial response after the switch. The patient with lymphoma demonstrated increased lymph-nodal uptake of the tracer on PET.

At univariate analysis, none of the demographic, clinical, laboratory and imaging predictors was significantly associated with the number of assessments when patients were in active disease nor were associated with the prednisone discontinuation at 12th month (Table III). A multivariate analysis was not performed because of the lack of significant associations at univariate analysis and for reasons related to the small sample size.

Table III. Univariate analysis including as predictors baseline demographic, clinical, laboratory and imaging features.

Dependent variable / Independent variable	Number of visits being in active disease (DAS28-CRP >2.6) *p*-values	Prednisone discontinuation after 12 months *p*-values	Complete oncologic response at follow-up	Disease progression at follow-up
Age	0.89	0.30	0.77	0.59
Sex	0.49	0.99	0.39	0.61
Extra-articular immune mediated toxicities	0.21	0.64	0.39	0.43
Tenosynovitis at US	0.31	0.35	0.15	0.84
Erosions at US	0.40	0.99	0.61	0.18
ANA positivity	0.58	0.64	0.83	0.43
ESR	0.67	0.88	0.87	0.90
CRP	0.71	0.48	0.17	0.63
DAS28-CRP	0.14	0.28	0.86	0.26

Discussion

Our retrospective longitudinal pilot study reported the articular and oncologic outcomes in ICI-IA treated with MTX. Patients were able to significantly reduce prednisone dosage to a target <5 mg daily which is a target dosage recommended by recent international guidelines (21). Due to the study design and the absence of a control group without MTX treatment, we cannot draw conclusions related to the oncologic safety of MTX but interestingly, in our cohort, cancer progression was observed in only 3 patients (21.5%) at follow-up.

Recent studies have shown that concurrent use of ICI and immunosuppressants, including oral GCs, csDMARDs and TNF-i, generally do not negatively impact cancer outcomes in patients who develop arthritis during ICI therapy (4). Although there are mixed reports regarding the impact of biological agents on arthritis management and cancer progression, several studies indicate that these treatments can be used safely in this setting although with varying rates of cancer progression (16–50%) (12, 22). Furthermore, anti-TNF agents such as infliximab, used concomitantly with ICIs like nivolumab and ipilimumab, have been found safe in managing rheumatic irAEs without compromising oncologic outcomes (23).

Conversely, higher doses of GCs have been associated with reduced survival in melanoma patients receiving ICI, indicating a potential negative impact of high-dose GCs on ICI efficacy (7). Additionally, anti-IL-6R blockers, such as tocilizumab, have been effective in treating ICI-induced polyarthritis, with evidence showing clinical improvement, reduced C-reactive protein levels, and shorter time to hospital discharge (24, 25).

Although MTX may be slower in achieving disease control compared to biological DMARDs such as TNF-I and IL-6R blockers, observational comparative data have shown that MTX might be safer in terms of oncologic outcomes (12). Another observational study has shown that patients treated with MTX for grade 3 ICI-induced arthritis showed positive outcomes in managing rheumatic disease while maintaining long-term cancer remission (26).

From a molecular perspective, indeed, previous evidence has shown that MTX exhibits both anti-inflammatory and anti-proliferative properties, primarily through increased adenosine release which inhibits inflammatory cytokines, and the inhibition of dihydrofolate reductase, which disrupts DNA synthesis and immune cell proliferation (27, 28).

Our findings, showing that patients were able to reduce GC use to recommended levels, are promising, especially considering the results already observed in a small sample size. In fact, if this significant effect is observed in a small cohort, it is plausible that similar or even stronger outcomes could be replicated in larger studies ongoing. To avoid strong immunosuppressive actions, a low dosage of MTX was used. This suggests that MTX could be an effective strategy for minimising GC usage at least in ICI-IA management, aligning with goals of reducing long-term GC-related adverse effects.

Considering these safety data and given that MTX is also more cost-effective compared to biologics, MTX might be considered a potential first choice among DMARDs for managing arthritis associated with ICI therapy.

Among the main limitations of the study, we acknowledge the retrospective observational design and the lack of a control group without MTX and/or treatment with another immunosuppressive drug which are not ideal for assessing the efficacy and safety of a drug. Another limitation is related to a small sample size of patients. Furthermore, our regression analysis did not identify significant predictors of outcomes, likely due to the limited sample size. This contrasts with recent literature, which suggests that higher baseline disease activity, presence of tenosynovitis, and longer duration of symptoms are associated with an increased need for DMARDs in managing ICI-IA (29). Lastly, synovial fluid analysis and synovial tissue biopsy were not performed in any patients, which might have provided additional insights into the inflammatory profile and underlying pathology of immune checkpoint inhibitor-induced arthritis, particularly in relation to macrophage activation/polarisation, and the presence of lymphocytic infiltrates in the synovium (30-32).

As a strength, this is one of the fewest longitudinal studies published in literature including multiple outcomes related both to the control of the inflammatory articular disease and oncologic outcomes, providing useful information for the clinicians managing these conditions.

Conclusions

The use of MTX in ICI-induced arthritis showed promising results in reducing GC dosages and managing articular

disease activity, with no major toxicities observed over one year.

Oncologic outcomes were varied, with the majority patients maintaining complete or partial responses. However, due to the lack of a control group, definitive conclusions about the efficacy and safety of MTX cannot be drawn.

These findings suggest that MTX may be a viable GC-sparing option in this context, but larger, controlled studies are needed to confirm these observations and better understand the impact on both articular and oncologic outcomes.

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