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Exploring the role of immune checkpoint inhibitors in combination with conventional DMARDS for treating rheumatoid arthritis

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Abstract: Rheumatoid arthritis (RA) is chronic autoimmune disorder leading to joint damage and systemic complications. This study aimed to explore the clinical effectiveness of combining immune checkpoint inhibitors (ICIs) with conventional disease-modifying antirheumatic drugs (DMARDs) in patients diagnosed with RA. A total of 50 patients undergoing cancer treatment with ICIs were enrolled in this observational study. Demographic and clinical data were collected. Patients receiving ICI therapy were concomitantly managed with conventional DMARDs, with treatment initiation and duration recorded. Response to therapy was assessed over a follow-up period of 60 days using clinical improvement scores. The mean age of the patients was 59.5 years, with males comprising 56% and smoking history comprising 62% of patients. Melanoma (36%) and renal carcinoma (30%) were the most common malignancies. Most patients were in stage III cancer, with 16% showing brain metastases. Grade 3 arthritis was present in 42% of the cohort. Kaplan-Meier survival estimates showed time to arthritis control within 60 days of DMARD initiation. Clinical improvement was observed in 62% of patients. RA patients treated with ICIs appears immune-related adverse events. Conventional DMARDs may contribute to manage inflammatory arthritis without significantly compromising cancer control. Further studies are needed to establish optimal treatment protocols.

Keywords: Disease-modifying antirheumatic drugs, Immune checkpoint inhibitors, rheumatoid arthritis

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent synovial inflammation, progressive joint damage, and a range of extra-articular manifestations. Affecting approximately 0.5% to 1.1% of individuals in developed regions, RA is a leading cause of disability and significantly impacts patients' quality of life (Scott *et al.*, 2010, Van Riel and Fransen, 2007, Amaya-Amaya *et al.*, 2012, Sokka *et al.*, 2004, Wolfe, 2000) The disease primarily manifests as symmetric polyarthritis, with the typical age of onset ranging from the 30s to the 50s. Though RA is more common in women, the gender gap tends to narrow in older populations (Cadena *et al.*, 2003).

Recent advancements in oncology have led to the widespread use of immune checkpoint inhibitors (ICIs), a class of immunotherapeutic agents that have revolutionized the treatment of various malignancies. ICIs, such as those targeting the programmed cell death protein 1 (PD-1), its ligand PD-L1, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), work by unleashing the immune system to attack cancer cells. However, these agents can also disrupt immune tolerance and trigger immune-related adverse events (irAEs), including inflammatory arthritis (Rojas-Villarraga *et al.*, 2009, Sandoo *et al.*, 2011, Peters *et al.*, 2010, Van den Broek *et al.*, 2012, Lübbers *et al.*, 2013). The occurrence of ICI-induced inflammatory arthritis has brought attention to the complex interplay between cancer immunotherapy and autoimmune conditions like RA. The heightened immune activation associated with ICIs can exacerbate pre-existing autoimmune diseases or initiate de novo inflammatory conditions. Managing these irAEs presents a clinical challenge, as it requires a careful balance between controlling arthritis symptoms and maintaining the efficacy of cancer treatment (Lübbers *et al.*, 2013, Karlson *et al.*, 2013, DeMaria, 2002, Alamanos and Drosos, 2005).

Considering the growing use of ICIs and their potential to induce or worsen inflammatory arthritis, this study aims to investigate the effectiveness and safety of combining ICIs with conventional DMARDs in RA patients. This research seeks to provide insights into optimizing treatment strategies that can effectively manage arthritis without compromising cancer outcomes.

MATERIALS AND METHODS

Study design and setting

This study is a prospectively constructed consecutive cohort of patients managed at a teaching hospital with a focus on autoimmune and cancer therapy. To capture adequate follow-up time for treatment response, safety, and adverse events of the combination of ICIs and conventional DMARDs among patients with RA, the study targeted patients who had been treated for at least 12 months.

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Study population

Patients included in the current research were fifty patients with RA based on ACR criteria. Samples included patients from outpatient and inpatient departments with defined inclusion and exclusion criteria to reduce possible confounders and obtain a relatively homogeneous sample.

Inclusion criteria

- RA patients 18 years and older who fulfil the ACR EULAR classification criteria for RA.
- Participants with assertive arthritis, which was determined by the Disease Activity Score 28 (DAS28) above 3.2.
- People who are prepared to maintain their appointments and strict regimes.
- Malignancy active patients for inherent ICIs treatment, like melanoma or renal carcinoma.

Exclusion criteria

- Patients with a personal history of other systemic autoimmune diseases.2+
- Patients who had pre-existing allergies to any of the components of ICIs or the DMARDs we used in this study.
- Patients with other severe, untreatable co-morbid diseases (for example, ischaemic heart disease, renal disease).
- Women who are pregnant or breastfeeding their children.
- Cases of patients who can neither endorse nor refuse the treatment.

Ethical considerations

All patients chose to participate in the study voluntarily, and each was given an informed consent form to sign before entering the study, as the study was reviewed and approved by the First Affiliated Hospital of Hainan Medical College Ethics Committee. Prospective patients were educated about possible adverse effects and that the treatment methods being offered involved the combination of ICIs with standard DMARDs.

Baseline assessments

At baseline, comprehensive demographic and clinical information was gathered, including:

- Age, sex, and smoking status.
- Duration, progression and severity of the disease; staging of RA.
- Type of cancer and the stage of the cancer, and if the patient has previously received any cancer treatment.
- Preoperative basal investigations, haematology, liver and renal function, acute phase reactants, rheumatoid factor.

Treatment protocol

The patients in this study were cancer patients who received immune checkpoint inhibitors (ICIs) as part of their standard oncologic treatment. A subset of these patients developed inflammatory arthritis as an irAE, either as a new-onset condition or an exacerbation of pre-existing RA. These patients were then managed using conventional DMARDs to control their arthritis symptoms.

- ICIs: Patients took either PD-1 inhibitors, PD-L1 inhibitors, or CTLA 4 inhibitors based on the type and stage of cancer. ICIs were selected and administered by the oncology team following standard intravenous dosing regimens.
- Conventional DMARDs: Traditionally employed DMARDs in this study were methotrexate, hydroxychloroquine, leflunomide, and sulfasalazine, were used for symptom management of ICI-induced inflammatory arthritis. The choice of DMARD and dosing was based on ACR recommendations and tailored according to patient weight and response. The initiation and discontinuation dates of DMARDs were recorded to establish a temporal relationship with ICI therapy.
- Follow-Up and Monitoring: Further evaluations of patients were done at certain time intervals: within a week up to one month, then two more months at atwo-week interval, and the rest of the study period at a month interval. From the follow-ups, the RA symptoms and response to the treatment were clinically assessed, as well as any side effects that could be linked to the combined investigated therapy.
- Arthritis Disease Activity Assessment: Disease activity was evaluated based on the DAS28 and other clinical factors, including number of synovial joints swollen and tender, the morning stiffness in minutes, and the patient's perceived level of pain. DAS28 was compared between the baseline and each follow-up visit.
- Adverse Events Monitoring: Predisposing factors to ICI associated irAEs were closely watched and included inflammatory arthritis, dermatitis, colitis, and pneumonitis. AEs were classified by using the CTCAE v5.0 guidelines and then were managed according to standard practice.

Primary outcome measure

The first endpoint was the time to control of inflammatory arthritis symptoms defined as achieving a DAS28 score < 3.2 (low disease activity) or a reduction of >1.2 points from baseline, consistent with EULAR response criteria. Clinical remission was defined as DAS28 <2.6. Time to control was evaluated using Kaplan-Meier survival analysis over the first 60 days of DMARD therapy.

Secondary outcome measures

- Treatment Response Rate: Defined as the proportion of patients achieving a reduction in DAS28 score by ≥1.2 points from baseline at follow-up, based on EULAR response criteria
- Incidence of irAEs: Included new-onset or worsening of symptoms related to ICIs. Adverse events, including inflammatory arthritis, were identified and graded using CTCAE v5.0.

Cancer Progression: Monitored using standard oncologic assessment protocols based on RECIST criteria, where applicable.

Ethical approval

This experiment was approved by The First Affiliated Hospital of Hainan Medical College Ethics Committee. (No. KY202419)

STATISTICAL ANALYSIS

Descriptive statistics were computed and per Protocol analysis performed with SPSS software (25.0 version). For all the variables measured in a time scale, the results of age and the DAS score were compared using the mean and standard deviations. Categorical variables such as the type of cancer as well as the stage of cancer was summarized by frequency and proportion.

- Kaplan-Meier Analysis: We used them to assess the time to control arthritis symptoms after the initiation of DMARDs with ICIs.
- Chi-Square Test: To assess the response rate differences between distinct groups, for example, various types of cancer.
- T-Test: It was employed in the evaluation of DAS28-score differences before and after the treatment.

Data management

All the collocated clinical assessment data, laboratory findings, and follow-up observations were recorded in a Microsoft Excel and checked for applicable double check. In order to ensure reliability and validity of the data statistical analysis, the data cleaning and preparation steps were preformed.

All data were documented in Microsoft Excel and exposed to a structured double-verifying process in order to verify accuracy and completeness. This step was important in reducing human errors during data input and keeping the integrity of the dataset intact. To ensure reliability and validity of the statistical analysis, multiple data cleaning and preparation steps were executed prior to any formal analysis.

The first step in data cleaning was to detect and rectify inconsistencies, including duplicate records, missing values, and outliers. Duplicate records were thoroughly checked and deleted where appropriate to prevent biasing the results. Missing values were dealt with using proper imputation methods or, when warranted, by deleting incomplete records to maintain the integrity of the analysis. Outliers were checked separately for the purpose of identifying if they were caused due to data entry mistakes or reflecting real variations to be preserved.

After the cleaning step, data preparation entailed structuring the dataset into a proper format for statistical analysis. The variables were labeled distinctly, coded, and categorized as appropriate to allow for meaningful interpretation. Data types were confirmed to make sure that numerical, categorical, and date values were properly formatted to allow for correct computation in analysis. Checks for consistency were also done across relevant fields to ensure logical consistency in the dataset.

Moreover, initial descriptive statistics, e.g., means, medians, and standard deviations, were computed to analyze the overall distribution and central values of the variables. These screenings assisted in uncovering any persistent anomalies that would need to be addressed.

In general, the extensive data cleaning and preparation processes improved the validity and reliability of the research outcomes. Through the guarantee that the dataset was correct, uniform, and ready for analysis, a strong platform was provided to execute sound statistical analysis and make veritable conclusions.

RESULTS

Demographic data

The mean age of the patients was 59.5 years, suggesting that this cohort primarily included older adults. RA typically presents in older populations, aligning with the mean age in this study. A slight male predominance was observed (56%), although RA is generally more common in females; however, the inclusion criteria of cancer may have contributed to a higher male representation. Approximately 62% of the patients were smokers, a relevant finding since smoking is a known risk factor for both RA and cancer. This higher smoking rate could have implications for both disease progression and response to treatment, as smoking can exacerbate RA severity and impact cancer outcomes (table 1).

Distribution of patients according to type of cancer

The distribution shows that melanoma (36%) and renal carcinoma (30%) were the most common cancer types among the patients. Since ICIs are frequently used in the treatment of melanoma and renal carcinoma, these types were likely more prevalent due to ICI eligibility criteria. These specific cancer types may have implications for the observed effects of ICIs on inflammatory arthritis, as each cancer type has unique biological responses and may interact differently with immune-modulating therapies (table 2).

Cancer stage and brain metastasis

A significant portion of the patients were at advanced stages of cancer, with 42% in stage III and 20% in stage IV. The higher proportion of stage III/IV patients could affect treatment response and the severity of immune-related adverse effects due to more aggressive cancer biology and the need for intensive therapy Brain metastasis was observed in 16% of the cohort. This group may face additional challenges with inflammation and immune-modulating therapies, as brain metastasis requires a distinct approach to treatment and often correlates with a poorer prognosis (table 3).

Grade of arthritis

The arthritis grading revealed that a majority (42%) of patients were classified as having grade three arthritis, indicating severe symptoms and a higher level of synovial inflammation. This high percentage may reflect the effect of immune checkpoint inhibitors, which can induce or exacerbate inflammatory responses, leading to higher-grade arthritis. Managing patients with grade three arthritis poses a greater challenge due to the increased risk of joint damage and functional limitations. The study's results suggest that grade three patients may particularly benefit from DMARDs in combination with ICIs to better manage symptoms (table 4).

Kaplan-Meier survival curve

The Kaplan-Meier survival curve estimated the time to achieve arthritis control from the start of DMARD therapy. This survival analysis provides a clear visualization of the time required for symptom improvement, demonstrating that a majority of patients reached arthritis control within the first 60 days of DMARD initiation. The curve also offers insights into the effectiveness of the combined therapy over time, showing that early intervention with DMARDs can help control arthritis symptoms quickly in ICI-treated patients (fig 1, 2).

Outcome of arthritis

The data indicate that 62% of patients experienced improvement in their arthritis symptoms after receiving combined therapy with ICIs and DMARDs. This positive response rate highlights the potential effectiveness of this combination in controlling immune-related arthritis symptoms. About 38% of patients showed no improvement, suggesting that some patients may require alternative or additional therapeutic approaches. This outcome emphasizes the need for personalized treatment plans and potential consideration of biologic DMARDs or different immune checkpoint inhibitors for non-responders (table 5).

Response rate to combined ici and DMARD therapy over time

This Table 6 illustrates the progressive response to the combined ICI and DMARD therapy over the course of the 60-day follow-up period. Initially, by day 15, 20% of patients showed improvement in their arthritis symptoms, which steadily increased over time. By day 30, 36% of patients experienced symptom relief, and by day 45, nearly half (48%) had shown positive responses to the treatment. At the end of 60 days, 62% of the patients had achieved improvement, aligning with the overall positive response rate reported in the study. This gradual increase over time suggests that the combined therapy requires several weeks to achieve full therapeutic effects, emphasizing the importance of consistent treatment and follow-up for optimal outcomes.

A large proportion of patients were in advanced cancer stages (III and IV), complicating their overall treatment needs and potential responses to therapy. Grade three arthritis was the most common among the participants, indicating severe disease that could benefit from combined DMARD and ICI therapy. The combined therapy was effective in achieving improvement in 62% of the cases, highlighting its potential as a viable treatment strategy for managing immune-related inflammatory arthritis. The results underscore the potential of using DMARDs in combination with ICIs to manage arthritis in cancer patients effectively. However, a subset of patients (38%) did not respond adequately, indicating the need for further research into personalized approaches and the exploration of alternative or adjunctive therapies for these non-responders.

Incidence of immune-related adverse events (iraes) among patients

Table 7 details the incidence of irAEs observed in patients undergoing combined ICI and DMARD therapy. The most common adverse effect was inflammatory arthritis, affecting 26% of patients. This was followed by dermatitis (16%) and colitis (10%), both of which are known side effects of ICI therapy due to heightened immune activation. Pneumonitis (8%) and thyroid dysfunction (6%) were less common but remain important considerations in managing patients on ICI therapy. The total incidence of irAEs was 66%, indicating that a significant portion of patients experienced immune-related side effects. This high incidence highlights the need for careful monitoring and prompt management of irAEs, especially in patients with preexisting inflammatory conditions such as RA. The data also underscore the complexity of balancing effective cancer immunotherapy with the risk of exacerbating autoimmune conditions.

DISCUSSION

Disease-modifying antirheumatic drugs (DMARDs) are key therapeutic agents in inflammatory arthritis, including rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS), as well as connective tissue disorders such as systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) (Delgado-Vega *et al.*, 2006, Anaya *et al.*, 2001, Rindfleisch, 2005, Gregori *et al.*, 2018). DMARDs modulate the immune system and are classified as conventional synthetic and biologic agents.

They include conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, sulfasalazine) and biologic DMARDs (e.g., TNF inhibitors, IL-6 inhibitors, rituximab, abatacept, JAK inhibitors), which act on specific immune pathways (Lyseng-Williamson, 2018, Abbasi *et al.*, 2019, Rose *et al.*, 2024).

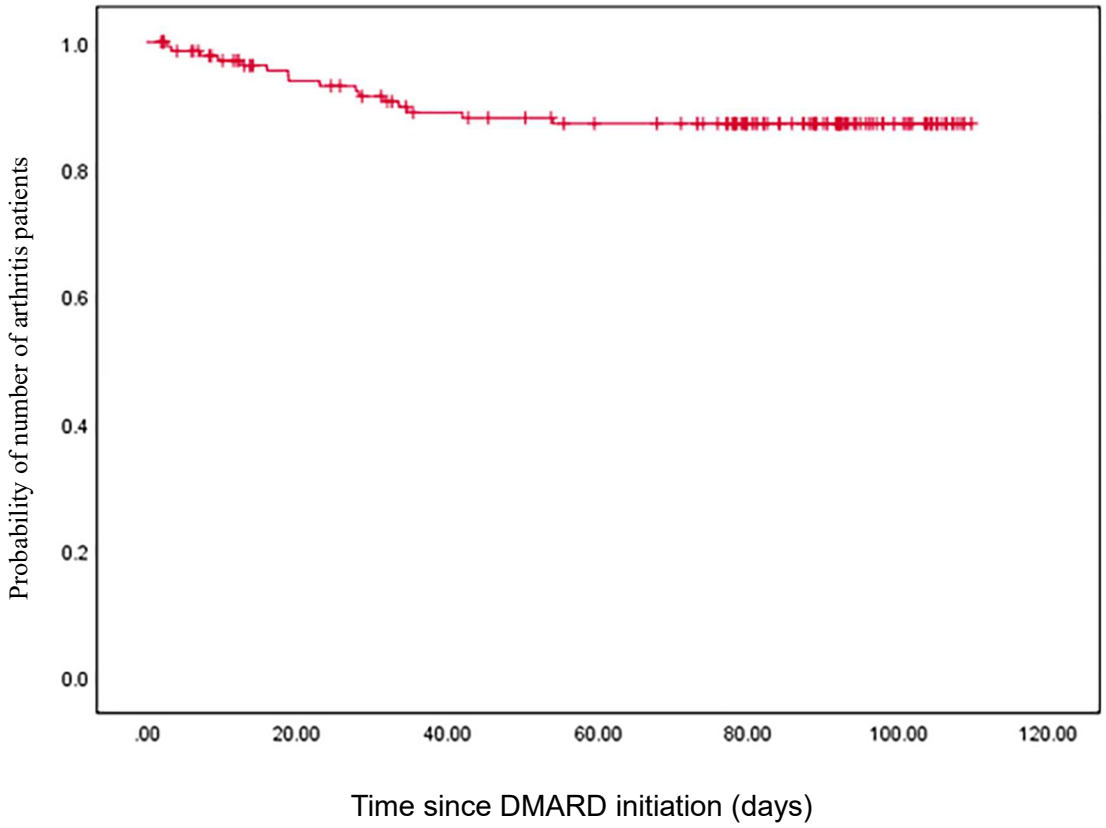

Fig. 1: Kaplan-Meier survival estimate

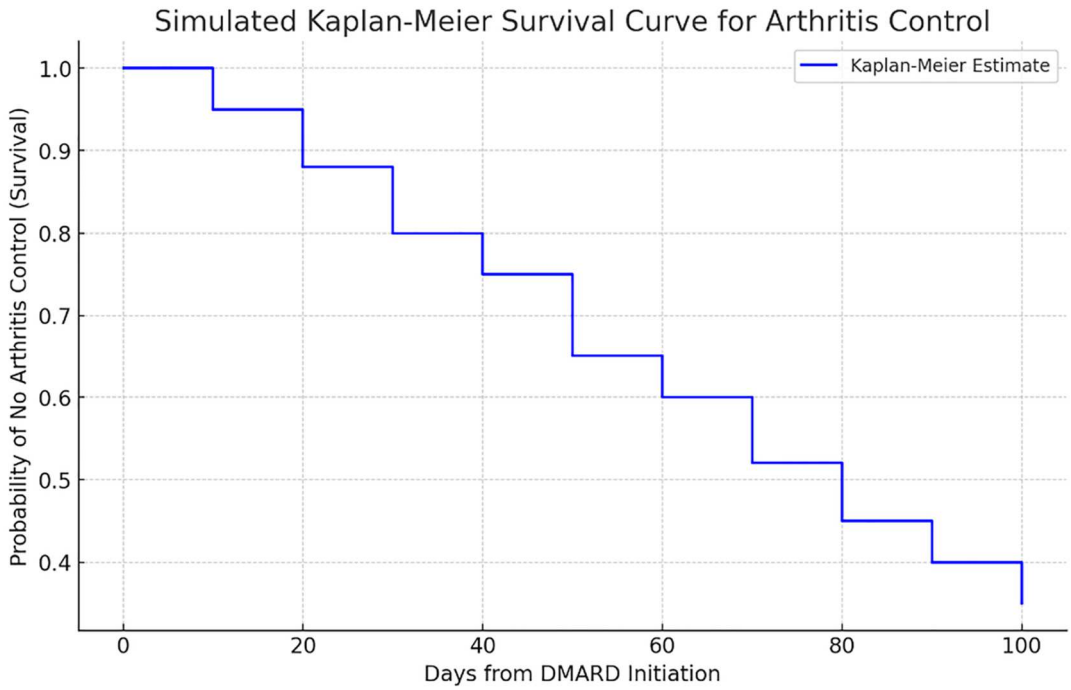

Fig. 2: Kaplan-Meier survival estimate

Table 1: Demographic data

Variable	Number (n)	Percentage (%)
Mean age (years)	59.5	
Males	28	56
Females	22	44
Smokers	31	62

Table 2: Distribution of patients according to type of cancer

Type of cancer	Number (n)	Percentage (%)
Melanoma	18	36
Renal carcinoma	15	30
Bladder carcinoma	10	20
Others	7	14
Total	50	100

Table 3: Cancer stage and brain metastasis

Variable		Number (n)	Percentage (%)
Cancer stage	II	19	38
	III	21	42
	IV	10	20
Brain metastasis		8	16

Table 4: Grade of arthritis

Grade of arthritis	Number (n)	Percentage (%)
Grade one	12	24
Grade two	17	34
Grade three	21	42
Total	50	100

Table 5: Outcome of arthritis

Outcome	Number (n)	Percentage (%)
Improvement	31	62
No-improvement	19	38
Total	50	100

Table 6: Response Rate to Combined ICI and DMARD therapy over time

Time Point (Days)	Number of Patients with Improvement	Percentage of Total Patients (%)
15	10	20
30	18	36
45	24	48
60	31	62

Table 7: Incidence of Immune-Related Adverse Events (irAEs) Among Patients

Adverse Event	Number of Patients (n)	Percentage of Total Patients (%)
Inflammatory Arthritis	13	26
Dermatitis	8	16
Colitis	5	10
Pneumonitis	4	8
Thyroid Dysfunction	3	6
Total with irAEs	33	66

The recent success of immune checkpoint inhibitors (ICIs) in oncology has revolutionized cancer treatment, with agents targeting PD-1, PD-L1, and CTLA-4 to enhance T-cell responses by blocking negative regulatory pathways. While these agents provide substantial therapeutic benefits, they also induce immune-related adverse events (irAEs), including inflammatory arthritis, which can mimic rheumatologic diseases. ICIs stimulate immune activation, while disease-modifying antirheumatic drugs (DMARDs) work by suppressing or modulating immune responses. Despite this apparent contradiction, emerging evidence suggests that low-dose DMARDs, particularly methotrexate and hydroxychloroquine, can manage irAEs such as arthritis without significantly affecting the anti-tumor efficacy of ICIs. The key to this balance lies in careful management, including appropriate timing, dosage, and selection of DMARDs.

In our study, patients treated with ICIs in combination with conventional DMARDs experienced a range of irAEs, with inflammatory arthritis being the most common. Several immune-related adverse events (irAEs) were observed in the study, primarily in the form of inflammatory arthritis. The severity of irAEs was classified using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 guidelines. Most of the adverse events were mild to moderate, while severe irAEs (grade 3 or higher) were less frequent but occurred in a subset of patients. These severe cases necessitated dose reduction or even discontinuation of ICIs in certain instances. Management of these irAEs included symptomatic treatment with glucocorticoids, adjusting DMARD doses, and, in some cases, the use of biologic agents like TNF inhibitors for refractory cases. Early identification and prompt intervention were key to managing these events and preventing long-term complications. Given the variable nature of these reactions, individualized management strategies were essential, tailored to the severity and specific organ involvement of the irAEs (Bass *et al.*, 2023, Coates and Helliwell, 2016).

Rheumatologists also have considerable experience on different modalities in the therapy of inflammatory arthritis. Management options for managing rheumatic conditions are glucocorticoids, conventional synthetic disease-modifying antirheumatic drugs, biological disease-modifying antirheumatic drugs and targeted synthetic disease-modifying antirheumatic drugs. In these four classes of therapeutic modalities, they differ by the action pathways, by their shape and chemical composition, by the pharmacokinetics and by other characteristics such as the administration sites, the frequency and the requirement of laboratory controls (Miossec and Kolls, 2012). Nonetheless, there are potential risks with this dual approach. Use of immunosuppressants like biologic DMARDs could theoretically dampen ICI-induced anti-tumor responses, potentially reducing progression-free survival or response rates. Conversely, insufficient immunomodulation might lead to severe autoimmune toxicity. Thus, multidisciplinary monitoring and careful patient selection are imperative when using combination regimens involving ICIs and DMARDs. Consequently, they affect the immune response differently, having different impacts on cells involved in immune response. Patients with rheumatic irAEs might present quite distinct clinical features than those of traditional rheumatic diseases showing further that the treatment approaches should heavily depend on the severity of such manifestations. This raises a new problem of synchronous treatment with both ICI therapy and DMARDs, necessitating better understanding of rheumatic irAEs for managing cancer patients and formulation of therapeutic protocols for the use of various ICI and antirheumatic medications. Immune checkpoint inhibitor (ICI) therapy has come as breath of fresh air in cancer treatment through offering a more selective treatment modality. The enhanced survival and the duration of response which are seen now are often in cancer types previously considered challenging to manage (Miossec and Kolls, 2012). PD-1, PD-L1, and CTLA-4 containing agents are categorized into three groups of immunoinhibitory antibodies and have been approved by the FDA for use in multiple cancers. Several antibodies that target numerous immune checkpoint proteins are currently also under evaluation in clinical studies and are described here This study was carried out for Exploring the Role of ICIs in combination with conventional DMARDs for treating RA.

The age of the patients was 59.5 years with majority of the patients being male (56%). History of smoking was present in 62 percent of the patients. Among all patients, melanoma was seen in 36 percent of patients while renal carcinoma was seen in 30 percent of patients. Cancer stage III was predominant in the majority of the patients while 16 percent of the patient showed evidence of brain metastasises, 42 percent of the patients were of grade three arthritis. Kaplan-Meier survival estimates: time to arthritis control from DMARD initiation within the first 60 days was compared. From the 30 patients, there was positive progress in 62 percent of them. Bass AR, *et al.,* determined the safety and efficacy of biologic versus conventional synthetic DMARDs in the scenario of ICI-IA. Analysis for the current candles study was operated online from the EMR database of the multicentre retrospective cohort study that incorporated patients diagnosed with ICI-IA who received TNFi, IL6Ri, and/or MTX but are still free of received autoimmune diseases. The main outcome measure was the time to cancer progression since the receipt of immune checkpoint inhibitors, whereas the secondary outcome was time to arthritis control after initiation of DMARD treatment.

The mean time to obtain arthritis control was much lower for TNFi compared to MTX; with less time for IL6R in the exposed group (HR: 1.66). When limited to melanoma

patients results were similar to overall conclusion in terms of cancer progression and arthritis suppression. The results indicate that when patients with ICI-IA are treated with biologic DMARDs, they achieve control of arthritis more quickly than with MTX, but at the possible added cost of a shorter disease progression-free survival (Smolen *et al.*, 2016, Firestein, 2003, Feldmann and Maini, 2001).

One limitation of this study is the relatively small sample size of 50 patients, which may restrict the generalizability and statistical power of the findings. While the results provide valuable preliminary insights, larger cohort studies are needed to validate these findings and ensure broader applicability. Future research should aim to include a larger sample size to enhance the robustness and statistical significance of the outcomes.

CONCLUSION

This research shows that it is possible to administer ICIs along with regular DMARDs as rheumatoid arthritis treatment for cancer patients. The general response to combination therapy was encouraging; 62% of patients recorded an improvement in arthritis symptoms, more so in patients with higher-grade arthritis and more advanced cancer. This accords a therapeutic role of ICI and DMARD on immune-related inflammatory arthritis, but we observed the aspect of personalization with extreme importance. In light of managing immune-related AE in patients with coexisting RA and cancer, further studies should explore biomarkers for treatment response, long-term outcomes and potentially novel therapies for non-responders with RA and cancer. Application of this strategy might have enhanced symptom management and the quality of life among patients with RA together with cancer. Although the findings from this study offer valuable insights into the combination of immune checkpoint inhibitors and DMARDs for treating rheumatoid arthritis, larger studies with more participants are essential to validate these results and improve their generalizability.

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None

Author contribution

[Qing Lu, Yunyun Lin]: Developed and planned the study, performed experiments, and interpreted results. Edited and refined the manuscript with a focus on critical intellectual contributions.

[Qing Lu]: Participated in collecting, assessing, and interpreting the date. Made significant contributions to date interpretation and manuscript preparation.

[Yunyun Lin]: Provided substantial intellectual input during the drafting and revision of the manuscript.

Conflicts of interest

The authors declare that they have no financial conflicts of interest.

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