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Invited Review

Immune Checkpoint Inhibitor-Induced Inflammatory Arthritis: Overview of Therapies and a Personalized Approach to Optimized Combined Therapy

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Abstract

Immune checkpoint inhibitors (ICIs), including anti-cytotoxic T lymphocyte antigen 4, anti-programmed cell death 1, and anti-programmed cell death ligand 1 (PD-L1) antibodies, are currently widely used in oncology clinical practice, achieving considerable success in improving disease outcomes. New checkpoint targets are being discovered and investigated through basic science research and clinical trials. ICI remove negative regulatory immune signals on T cells, leading to immune activation and induction of antitumor immunity. Patients who receive ICI, however, are at risk for developing immune-related adverse events (irAEs), which are attributed to increased T cell activity against antigens in both tumors and in healthy tissues, to increased inflammatory cytokine levels, to increased levels of preexisting autoantibodies, and to enhanced complement-mediated inflammation. Arthritis is one of the most common irAEs. ICI-induced rheumatic irAEs are categorized by levels of severity which guide the choice of treatment options. Management of ICI-induced rheumatic irAEs includes the use of glucocorticoids, disease-modifying antirheumatic drugs (mainly methotrexate), and biological agents (e.g., tumor necrosis factor, interleukin-6 receptor, and CD20 inhibitors). This review aims to summarize the current ICI subtypes, their role in rheumatic irAEs development, and therapies currently used in clinical practice to manage irAEs. In addition, we propose to use an ex vivo personalized diagnostic assay for the selection of the most effective ICI with antirheumatic drugs combinations that will inhibit the advancement of ICI-induced adverse events.

Keywords: Immune checkpoint inhibitor (ICI), immune-related adverse events (irAEs), ICI-induced inflammatory arthritis, disease-modifying anti-rheumatic drugs (DMARDs), combined ICI and DMARD therapies

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Introduction

The advent of immune checkpoint inhibitors (ICIs) caused a paradigm shift in improving cancer therapy. ICIs comprise a novel class of immunotherapeutic drugs whose application continues to expand. However, ICI therapy is associated with excessive nonspecific immune activation and autoimmune response that result in immune-related adverse events (irAEs). Immune-related adverse events can cause clinically severe rheumatic disease manifestations. Rheumatologists are highly experienced in the use of available multiple therapeutics for controlling inflammatory arthritis. Efficient therapies for rheumatic diseases include glucocorticoids (GCs), conventional disease-modifying antirheumatic drugs (cDMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs). Each of these therapies differs in its mechanisms of action, structure, pharmacokinetics, and other characteristics, such as route and frequency of administration and need for laboratory monitoring. As such, they modulate the immune response differently. The manifestations of rheumatic irAEs can differ widely from those of classical rheumatic diseases, emphasizing the necessity for treatment individualization based upon symptom severity. The combination of ICI therapy with DMARDs represents a new therapeutic challenge and the need for increasing the knowledge regarding rheumatic irAEs in cancer patient management and developing relevant therapeutic guidelines for cotreatment with multiple choices of ICI and antirheumatic drugs.

Immune Checkpoint Inhibitor Subtypes

Immune checkpoint inhibitor (ICI) therapy has revolutionized cancer treatment by providing a more targeted therapeutic approach. Improved survival and prolonged responses are now being witnessed in previously difficult-to-treat malignancies. Three ICI groups consisting of programmed cell death protein 1 (PD-1),

Table 1. Severity Scale for Immune Reaction Adverse Effects According to The Common Terminology Criteria for Adverse Events (CTCAE) Version 5

	Grade 1	Grade 2	Grade 3	Grade 4
CTCAE V5 classification	Mild, asymptomatic, or mild symptoms, intervention not indicated	Moderate noninvasive intervention indicated	Severe or medically significant	Life-threatening consequences, urgent intervention required
Treatment	NSAIDs, corticosteroid injection	Referral to rheumatologist, intra-articular injection	Prednisone + MTX/TNF inhibitors, consider DMARDs	Hold ICI therapy immediately, treat rheumatic disease directly
Continue ICI?	Yes	Yes	Yes, consider pausing	No
Rheumatology consult?	No	Yes	Yes	Yes

programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors have been approved by the U.S. Food and Drug Administration for the treatment of various cancer types. In addition, several antibodies that target various immune checkpoint proteins are being assessed in clinical trials, and these subtypes are summarized here.

Anti-PD-1/Anti-PD-L1 Antibodies

Programmed cell death protein 1 and its ligand PD-L1 have been identified as a set of immune checkpoints that mediate coinhibitory signals to T-cell activation. Anti-PD-1 and anti-PD-L1 antibodies operate by blocking the interaction of PD-1 and PD-L1, thereby removing their inhibition on $CD8^+$ T cells and enhancing antitumor activity in peripheral tissues. These therapies have induced clinical responses of tumor regression across a variety of malignancies, including melanoma, renal cell carcinoma, non-small cell lung cancer, and bladder cancer.[1] Current anti-PD-1 therapies, including pembrolizumab, nivolumab, and cemiplimab, have shown significant effects in targeting a variety of malignancies through generating an antitumor response.[2] Anti-PD-L1 therapies, including atezolizumab, avelumab, and durvalumab, have additionally played a significant role in tumor reduction, especially notable in hepatocellular carcinoma and triple-negative breast cancer.[3] Most cancer patients, however, rely upon combination therapies that target both anti-PD-1 and anti-PD-L1 pathways in addition to chemotherapy, radiation, or other ICIs for optimal clinical outcomes.

Anti-CTLA-4 Antibodies

Cytotoxic T-lymphocyte-associated antigen 4 has been identified as an additional immune checkpoint target that serves as a negative regulator for T-cell immune response. Unlike PD-1/PD-L1, CTLA-4 regulates T cells during preliminary immune responses, primarily within the lymph nodes. Cytotoxic T-lym phocyte-associated antigen 4 competes with CD28 for B7 binding on antigen-presenting cells (APCs) in order to limit T-cell survival and induce T-cell anergy. In addition, expression of CTLA-4 on regulatory T cells (Tregs) plays an important role in the peripheral immune response against encountered foreign pathogens. Ipilimumab, the most prominent anti-CTLA-4 therapy, has shown improved outcomes in patients with melanoma and hepatocellular carcinoma.[4,5]

Anti-LAG-3 Antibodies

The lymphocyte activation gene 3 (LAG-3) is the newest anticancer immunotherapy target. LAG-3 is an inhibitory receptor involved in CD4/CD8 T-cell activation and also serves as a key regulator within the immune system. In conjunction with TCR/CD3 signaling, LAG-3 downregulates TCR activation, thereby inhibiting immune-mediated T-cell responses by binding to MHC class II. Programmed cell death protein 1 and LAG-3 exhibit significant similarities in their ability to regulate the tumor microenvironment and promote immune evasion.[6] Clinical trials aim at targeting these immune checkpoints simultaneously in order to determine their therapeutic benefits in combination. Novel anti-LAG-3 antibodies have shown promising results in delaying tumor growth, with greater effects seen by the combination of anti-LAG-3/anti-PD-1 therapies within solid tumors.[7] Anti-LAG-3 therapies are currently being explored in a variety of neoplasms, including, but not limited to, brain, head and neck, endocrine, lung, abdominal, urogenital, breast, and lymphoid tumors.[8]

Anti-TIM-3 Antibodies

T-cell immunoglobulin mucin domain-containing protein 3 (TIM-3) may be found on the surface of Th1 cells, a subtype of $CD4^+$ effector T cells that promote cellular-mediated immune responses. Specifically, TIM-3 mediates Th1 apoptosis through binding to galectin 9 (Gal-9).[9] Dendritic and natural killer cells constitutively express TIM-3 and may provide an alternative route for future immune checkpoint blockade therapies.[9] Clinical trials targeting TIM-3 have yielded encouraging results, particularly in solid tumors and liver cancer.[10] The use of combination blockade therapy against PD-1/TIM-3 reportedly achieves greater tumor control than individual ICI therapy.[11] Preclinical models have shown the potential of anti-TIM-3 therapy to reduce tumor progression and improve antitumor T-cell responses in a variety of cancer patients.[12]

Anti-TIGIT Antibodies

T cell immunoglobulin and ITIM domain (TIGIT) binds to 2 ligands, CD155 (poliovirus receptor, PVR) or CD112 (PVRL2 or Nectin-2), expressed by tumor cells and APCs within the tumor microenvironment.[13] It follows, therefore, that targeting this immune checkpoint may promote immune-mediated tumor rejection. Anti-PD-1 and anti-TIGIT combined therapy was observed to enhance $CD8^+$ T cells and $CD8^+$ tumor-infiltrating lymphocytes (TILs) in melanoma patients.[14] Murine models have demonstrated the primary mechanism of TIGIT antitumor signaling to involve regulatory T cells and to show coinhibitory responses with TIM-3 targets.[15] Preclinical studies have supported the use of TIGIT blockade monotherapy in addition to combined therapies with other ICIs.[16] The interim results of clinical trials on TIGIT blockades in cancer have favored the use of anti-PD-1/anti-TIGIT therapies in patients with solid malignancies.[17]

Anti-VISTA Antibodies

V-domain Ig suppressor of T-cell activation (VISTA), a member of the B7 family, has a unique ability to bind to overlapping sites on the extracellular domain. Binding to P-selectin glycoprotein ligand 1 (PSGL-1) and the V-Set and Immunoglobulin domain-containing VSIG-3 resulted in T-cell function inhibition. VISTA may also upregulate macrophages for cytokine release and increase IL-10 production.[18] The role of VISTA in both innate and adaptive immunity makes it a unique target for

cancer immunotherapies.[19] The VISTA protein expression in tumor cells had already shown a favorable prognosis in patients with pancreatic cancer who were treated with anti-VISTA antibodies.[20] Dual inhibitors of VISTA and PD-L1 in phase I/II clinical trials have additionally shown clinical efficacy in solid tumors.[21] VISTA biomarkers therefore comprise important candidates for use in cancer therapy.

Treatment Approach to Immune-Related Adverse Events

While ICI therapies show promising results, it should be borne in mind that their activity can lead to irAEs that may affect any organ system, most notably impacting the gut, skin, endocrine glands, liver, and lungs, as well as the musculoskeletal system.[22] The proposed mechanisms of action of irAEs include increased T-cell activity against antigens in tumors and healthy tissues, increased inflammatory cytokine levels, increased levels of preexisting autoantibodies, and enhanced complement-mediated inflammation due to direct CLTA-4 binding on normal tissue.[23] The incidence of ICI-induced arthralgia has been reported as high as 43%, and that inflammatory arthritis occurs in approximately 7% of patients.[24,25]

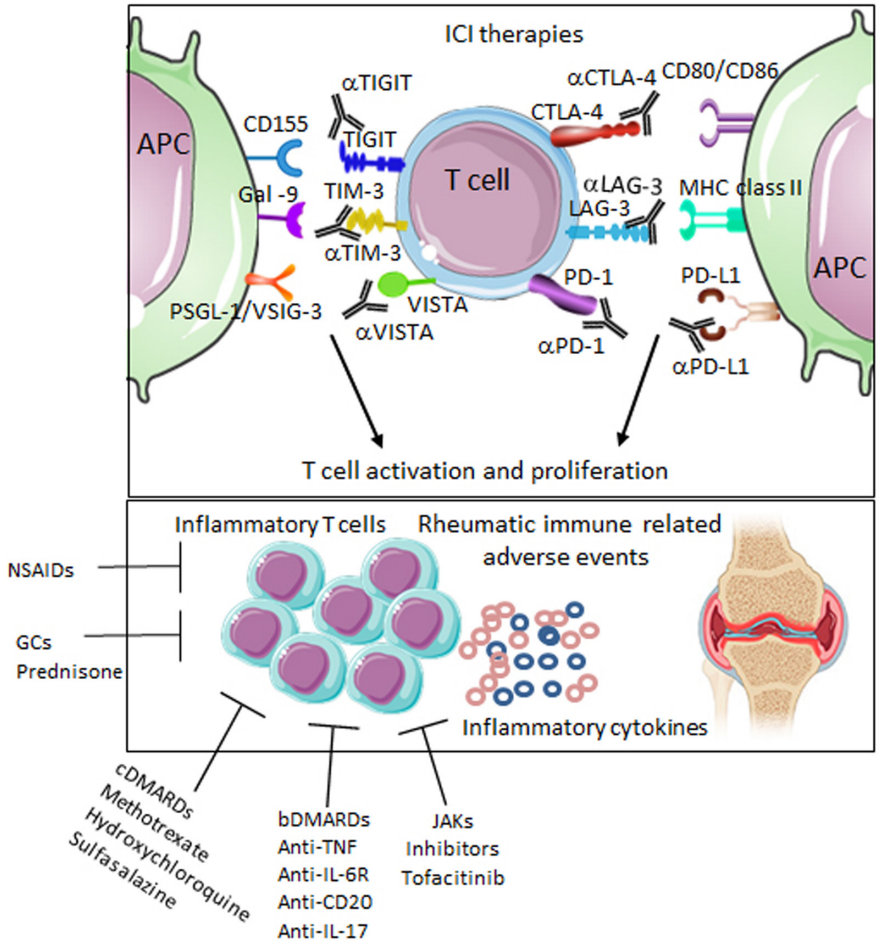

Figure 1. Immune checkpoint inhibitor therapy augments T-cell proliferation and activation, inducing rheumatic adverse events, and the potential of diverse antirheumatic drugs to block the excessive immune response. (Top) Immune checkpoint inhibitor therapies block inhibitory receptors, including antibodies against PD-1, PD-L1, CTLA-4, TIM-3, LAG-3, TIGIT, and VISTA. These inhibitory receptors contribute to T-cell dysfunction in cancer. As a result of their blockade, activation and proliferation of T cells induce ICI rheumatic irAEs. (Bottom) The excessive immune response and inflammatory cytokines can be blocked by diverse antirheumatic drugs, including NSAIDs, GCs, cDMARDs, and Janus kinase (JAK) inhibitors. APC, antigen-presenting cell; CD, cluster of differentiation; CTLA-4, Cytotoxic T-lymphocyte-associated antigen; Gal-9, galectin 9; GCs, glucocorticoids; ICI, immune checkpoint inhibitor; IL, interleukin; LAG-3, lymphocyte activation gene 3; MHC class II, major histocompatibility complex class II; NSAIDs, nonsteroidal anti-inflammatory drugs; PD-1, programmed death protein 1; PD-L1, programmed death ligand; PSGL-1, P-selectin glycoprotein ligand 1; R, receptor; TIGIT, T-cell immunoglobulin and ITIM domain; TIM-3, T-cell immunoglobulin mucin domain-containing protein 3; TNF, tumor necrosis factor; VISTA, V-domain Ig suppressor of T-cell activation; VSIG-3, V-Set and Ig domain-containing 3.

ICI-induced inflammatory arthritis (ICI-IA) may present in a variety of ways, including polyarthritis, mono- or oligoarthritis, and polymyalgia rheumatica-like syndrome.[25] Unlike other irAEs, ICI-IA can persist after immunotherapy discontinuation, causing irreversible joint damage and significant disability.[26] The European League against Rheumatism (EULAR) recommends treating ICI-induced irAEs initially with nonsteroidal anti-inflammatory drugs (NSAIDs) and/or analgesics for mild-to-moderate rheumatic irAEs (Table 1) (adopted from[27]). Treatment with systemic and/or intra-articular glucocorticoids is recommended in cases of insufficient response and persistent joint inflammation. However, it was recently shown that CTLA-4 and PD-1 inhibitor therapy preferentially enhanced Th17 cell signatures, thus contributing to steroid resistance in arthritis irAEs.[28] Conventional synthetic DMARDs (csDMARDs), such as methotrexate, can be considered in more severe cases of rheumatic irAEs. Numerous biologic agents targeting pro-inflammatory key cytokines [such as tumor necrosis factor (TNF), IL-6, IL-17, and IL-12/23] and immune cells (such as B cells) or targeted synthetic tsDMARDs, such as Janus kinase (JAK) inhibitors, have been proven effective with an acceptable safety profile for treatment of rheumatic diseases. The potential of the various ICI to activate the immune response that may eventually result in rheumatic irAEs and the potential of the above-listed antirheumatic drugs by their ability to mitigate the ICI-induced rheumatic irAEs are shown in Figure 1.

Evidence for ICI Use in Animal Models

Humanized BALB/c-hPD-1/hCTLA-4 mice were injected with vehicle or collagen-specific antibodies in order to induce rheumatic irAEs. The mice were treated with the ICI therapies, including ipilimumab, anti-human CTLA-4, and nivolumab, anti-human PD-1. The induced clinical arthritis was subsequently treated with anti-TNF, which produced significant mitigation of disease.[29] These findings support the use of targeted treatment with antirheumatic drugs against irAEs.

Evidence for ICI Use in In Vitro Models

Several in vitro studies have provided evidence for personalized use of combined antirheumatic drugs and ICIs to mitigate the development of rheumatic irAEs. Synovial fluid mononuclear cells were collected from rheumatic patients and the effect of pembrolizumab-induced immune reactions was tested without and with antirheumatic drugs in vitro. Pembrolizumab significantly increased monocyte chemoattractant protein 1 (MCP-1)

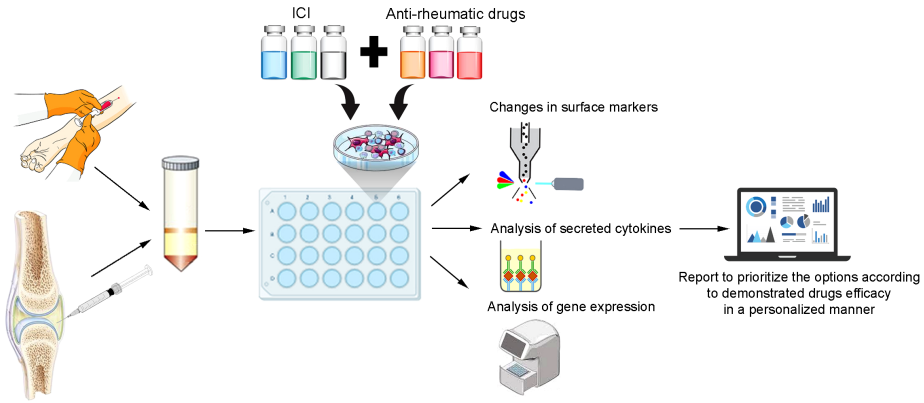

Figure 2. An ex vivo model may assist clinical decisions to prioritize ICI and antirheumatic drugs treatment in a personalized manner. The assay will enable assessment of immune response to drugs in ex vivo conditions on patients' own immune cells and to prioritize drug combinations based upon their potential effect. ICI, immune checkpoint inhibitor.

production in synovial cells, suggesting that anti-PD-1 can increase the monocyte activation that is involved in inflammatory arthritis induction. Coculture of synovial cells with pembrolizumab and anti-TNF, as opposed to anti-IL-6 receptor, downregulated the inflammatory monocyte activity.[30] A similar study tested the effect of anti-TNF and JAK inhibitors on cytotoxic $CD8^+$ T cells, which are adaptive immune cells and highly powerful effectors of the anti-cancer immune response. In vitro tofacitinib and infliximab treatment maintained the immune-metabolic profile and did not alter the capacity to release cytokines. Specifically, $CD8^+$ T cells continued to release cytokines and prevented the growth of the cultured human cancer cell line growth.[31] The use of anti-TNF additionally showed reduced tumor-specific activation of $CD8^+$ T cells, tumor-infiltrating lymphocytes (TILs), and of $CD8^+$ T cells derived from peripheral blood after incubation with autologous metastatic melanoma tumors from 2 patients.[32]

Evidence for ICI Use in Clinical Studies

Several clinical trials and studies have demonstrated the safe and efficacious use of concurrent ICI and antirheumatic therapies. Treatment of rheumatic irAEs is based upon The Common Terminology Criteria for Adverse Events (CTCAE), version 5, severity scale (Table 1). Patients with anti-CTLA-4/anti-PD-1-induced grade 1 inflammatory arthritis concomitantly treated with NSAIDs had preserved the antitumor effects of the ICIs.[33] Patients treated with ICIs together with systemic GCs (injection of 20-30 mg and systemic 6-week tapered dose of 2.5 mg) for grade 1 inflammatory arthritis showed a decreased cancer burden by positron emission tomography–computed tomography following the addition of GC treatment.[34] The use of hydroxychloroquine as monotherapy combined with a tapering dose of GCs also showed efficacious results as first-line therapy for patients with ICI-IA.[35] There are conflicting testimonies for the use of biological agents to combat arthritis and their effects on the progression of cancer. However, the use of NSAIDs, oral GCs, csDMARDs, and anti-TNF showed no negative impact on cancer outcomes in a cohort of 69 patients who developed arthritis during ICI treatment.[26] However, Faje et al reported that melanoma patients who received higher GCs doses (above the daily dose of 7.5 mg prednisone) had reduced survival compared to those who received a low dose. Theirs was the first study to demonstrate a potential negative effect of high GCs doses on the efficacy of ICI.[36]

Grade 3 ICI-induced arthritis treated with methotrexate showed a similar positive result in managing the rheumatic disease concurrently with anti-cancer treatment and long-term cancer remission.[34] Patients treated with nivolumab and ipilimumab and who developed arthritis manifestations received anti-TNF (infliximab and certolizumab), and the addition of infliximab concomitantly with nivolumab and ipilimumab was found to be safe.[37] However, patients treated with certolizumab and concomitant ICI therapy demonstrated a higher toxicity profile.[37] An additional study showed an 80% improvement of rheumatic irAEs in cancer patients treated with anti-TNF therapy, with evidence of cancer remission in 40% of patients.[38] The use of anti-IL-6 receptor (tocilizumab) has also been effective in combating rheumatic irAEs. All 3 patients with ICI-induced polyarthritis reported by Kim et al responded favorably to tocilizumab.[39] In a larger study, 87 patients with ICI-induced arthritis improved with GCs and anti-IL-6 receptor therapy as measured by C-reactive protein levels, clinical improvement, and time to hospital discharge.[40] Of note, anti-TNF and anti-IL-6 receptor were found to be more effective for ICI-induced arthritis compared to methotrexate, whereas cancer progression was significantly shorter for the former than for the latter.[41] Another study revealed improved clinical outcomes for ICI-induced colitis and arthritis in patients treated with anti-IL-6 receptor.[42] Anti-IL-17A may be another potential treatment of irAEs, as demonstrated in 2 patients with metastatic melanoma effectively treated with anti-IL-17A for ICI-induced arthritis.[43]

Patients with preexisting rheumatic diseases require additional monitoring since treatment with ICIs may lead to more adverse events. These patients reportedly experienced flares 40% more often than those with nonrheumatic autoimmune disorders, but the concurrent administration of ICIs and methotrexate was safe and did not diminish the efficacy of immunotherapy.[44] This finding has been supported by the results of the combined administration of hydroxychloroquine and sulfasalazine; however, further studies are needed to assess the use of biologic DMARDs in the treatment of irAEs in cancer patients.[45] A wide array of clinical evidence supports the concurrent use of ICI with antirheumatic therapies to combat irAEs. Given the results of the above-cited studies, it is clear that an individualized approach will assist in optimizing the quality of treatment.

Ex Vivo Personalized Assay for Optimized Selection of Antirheumatic Drugs to Inhibit ICI-Induced irAEs

Personalized Medicine Approach for Selection of ICI and Antirheumatic Drug Combinations

Immune checkpoint inhibitor therapy aims to reverse the "exhausted" state of immune cells in cancer and to turn on the immune response by over-activating immune cells that attack the tumor, the latter occasionally inducing autoimmune disease-like symptoms as a side effect. In contrast, antirheumatic drugs aim to suppress an excessive immune response. These therapeutic activities of 2 opposing drug groups can lead to unexpected clinical outcomes. In parallel, the variability in the immune response toward combined ICI and antirheumatic drugs seems to be dependent upon both drug-specific and patient-specific factors. In fact, the development of rheumatic disease-like symptoms is intrinsic and unique to each patient. The variability of drugs available for treatment poses an urgent unmet need to find predictive assays to facilitate therapy selection to reduce irAEs in ICI-treated patients.

An ex vivo assay approach based upon the response of a patient's own cells with the candidate drug combinations can detect the synergistic effect of those drugs, indicate the need for individualized adjustment of drug concentrations, or alternatively, identify nonresponse to specific drug combinations. For example, approximately 30%-40% of rheumatic disease patients do not respond to anti-TNF therapy. Ohman et al observed that treatment with infliximab reduced the frequencies of activated T cells ($CD25^+$ T cells) in patients with ulcerative colitis who responded to infliximab but not in nonresponders.[46] These markers were also reduced in ex vivo cultured peripheral blood cells incubated with infliximab, again differentiating between responders and nonresponders to treatment[47] and indicating that T-cell activation markers may predict response to treatment by means of anti-TNF agents. We had previously shown that different biological agents uniquely affected the activation and proliferation of lymphocytes derived from psoriatic arthritis (PsA) patients. Only anti-TNFs reduced the activation and proliferation of T cells ex vivo, while anti-IL-17A and anti-IL-6 receptor did not.[48] Moreover, anti-TNF exhibited selective activity on synovial fluid mononuclear cells derived from PsA and RA patients that was not mediated by other therapeutic drugs (i.e., GCs or other biologic DMARDs).[49] As such, we were able to show that diverse biologic agents acted differently on essential immune populations and inflammatory mediators participating in the immune response.

The current approach for treating rheumatic irAEs induced by ICIs is based on case reports and expert opinion. There are no validated diagnostic assays to guide clinicians in selecting the most effective combination therapies to reduce rheumatic irAEs of patients undergoing ICI therapy. The expansion of immunotherapy and available drug targets necessitates more accurate methods for optimal management of combined therapy for ICI-treated patients who develop irAEs.

Development of an Ex Vivo Model to Assist in the Selection of Combined Therapies

ICI-induced rheumatic irAEs represent a new disease entity, and not much is known about the modulation of the inflammatory response with combined ICI therapy and antirheumatic drugs. An ex vivo model may provide a useful tool for the evaluation of combined ICI+DMARDs activity on diverse immune biomarkers with the aim of identifying patients' response to these drugs. A proposed ex vivo model for the evaluation of patients' immune cell response to ICI and antirheumatic drugs is shown in Figure 2. Patients who may profit from this assay include: (i) ICI-treated patients with irAEs who are candidates to receive combined ICI + antirheumatic drug therapy, and (ii) patients with preexisting rheumatic diseases who develop cancer and need to initiate ICI therapy.

Conclusion

Immune checkpoint inhibitors are the standard of care for the treatment of several cancers, but they upregulate the immune system and consequently can result in off-target immune-related adverse events (irAEs). One of the most disabling irAEs is immune-related inflammatory arthritis. Rheumatic irAEs deleteriously affect the quality of life and occasionally lead to discontinuation of ICI treatment. Careful selection of appropriate DMARDs for the management of rheumatic irAEs under ICI therapy poses a major clinical challenge.

The concept of ex vivo testing of combined therapies with the aim of reducing ICI-induced rheumatic irAEs, in a personalized manner, aims at selecting best therapeutic choice of cancer treatment in combination with antirheumatic drugs to mitigate rheumatic irAEs while maintaining ICI efficacy. The assay evaluates simultaneously the patient's cells' immune response to multiple drug combinations. Its readout should be assessed in close collaboration between oncologists and rheumatologists. This platform could potentially prevent exposure to drug-induced clinically significant side effects. Further research is required to calibrate and validate the proposed model.

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References

1. Wu X, Gu Z, Chen Y, et al. Application of PD-1 blockade in cancer immunotherapy. *Comput Struct Biotechnol J*. 2019;17:661-674. [CrossRef]
2. Barrios DM, Do MH, Phillips GS, et al. Immune checkpoint inhibitors to treat cutaneous malignancies. *J Am Acad Dermatol*. 2020;83(5):1239-1253. [CrossRef]
3. Zerdes I, Matikas A, Bergh J, Rassidakis GZ, Foukakis T. Genetic, transcriptional and post-translational regulation of the programmed death protein ligand 1 in cancer: biology and clinical correlations. *Oncogene*. 2018;37(34):4639-4661. [CrossRef]
4. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711-723. [CrossRef]
5. Yau T, Kang YK, Kim TY, et al. Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: the CheckMate 040 randomized clinical trial. *JAMA Oncol*. 2020;6(11):e204564. [CrossRef]
6. Woo SR, Turnis ME, Goldberg MV, et al. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. *Cancer Res*. 2012;72(4):917-927. [CrossRef]
7. Yu X, Huang X, Chen X, et al. Characterization of a novel anti-human lymphocyte activation gene 3 (LAG-3) antibody for cancer immunotherapy. *mAbs*. 2019;11(6):1139-1148. [CrossRef]
8. Sauer N, Szlasa W, Jonderko L, et al. LAG-3 as a potent target for novel anticancer therapies of a Wide Range of tumors. *Int J Mol Sci*. 2022;23(17) [CrossRef]
9. Zhao L, Cheng S, Fan L, Zhang B, Xu S. TIM-3: an update on immunotherapy. *Int Immunopharmacol*. 2021;99:107933. [CrossRef]
10. Qin S, Xu L, Yi M, Yu S, Wu K, Luo S. Novel immune checkpoint targets: moving beyond PD-1 and CTLA-4. *Mol Cancer*. 2019;18(1):155. [CrossRef]
11. Martinez M, Kim S, St Jean N, et al. Addition of anti-TIM3 or anti-TIGIT antibodies to anti-PD1 Blockade Augments human T cell Adoptive Cell Transfer. *Oncoimmunology*. 2021;10(1):1873607. [CrossRef]
12. Acharya N, Sabatos-Peyton C, Anderson AC. Tim-3 finds its place in the cancer immunotherapy landscape. *J Immunother Cancer*. 2020;8(1) [CrossRef]
13. Chauvin JM, Zarour HM. TIGIT in cancer immunotherapy. *J Immunother Cancer*. 2020;8(2) [CrossRef]
14. Chauvin JM, Pagliano O, Fourcade J, et al. TIGIT and PD-1 impair tumor antigen-specific CD8(+) T cells in melanoma patients. *J Clin Invest*. 2015;125(5):2046-2058. [CrossRef]
15. Kurtulus S, Sakuishi K, Ngiow SF, et al. TIGIT predominantly regulates the immune response via regulatory T cells. *J Clin Invest*. 2015;125(11):4053-4062. [CrossRef]

16. Liu L, You X, Han S, Sun Y, Zhang J, Zhang Y. CD155/TIGIT, a novel immune checkpoint in human cancers (Review). *Oncol Rep*. 2021; 45(3):835-845. [CrossRef]
17. Ge Z, Peppelenbosch MP, Sprengers D, Kwekkeboom J. TIGIT, the next step towards successful combination immune checkpoint therapy in cancer. *Front Immunol*. 2021;12:699895. [CrossRef]
18. Yuan L, Tatineni J, Mahoney KM, Freeman GJ. VISTA: a mediator of quiescence and a promising target in cancer immunotherapy. *Trends Immunol*. 2021;42(3):209-227. [CrossRef]
19. ElTanbouly MA, Croteau W, Noelle RJ, Lines JL. VISTA: a novel immunotherapy target for normalizing innate and adaptive immunity. *Semin Immunol*. 2019;42:101308. [CrossRef]
20. Hou Z, Pan Y, Fei Q, et al. Prognostic significance and therapeutic potential of the immune checkpoint VISTA in pancreatic cancer. *J Cancer Res Clin Oncol*. 2021;147(2):517-531. [CrossRef]
21. Tagliamento M, Bironzo P, Novello S. New emerging targets in cancer immunotherapy: the role of VISTA. *ESMO Open*. 2020;4(suppl 3): e000683. [CrossRef]
22. Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. *Eur J Cancer*. 2016;54:139-148. [CrossRef]
23. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018; 378(2):158-168. [CrossRef]
24. Cappelli LC, Gutierrez AK, Bingham CO, 3rd, Shah AA. Rheumatic and musculoskeletal immune-related adverse events due to immune checkpoint inhibitors: a systematic review of the literature. *Arthritis Care Res (Hoboken)*. 2017; 69(11):1751-1763. [CrossRef]
25. Ghosh N, Tiongson MD, Stewart C, et al. Checkpoint inhibitor-associated arthritis: a systematic review of case reports and case series. *J Clin Rheumatol*. 2021;27(8):e317-e322. [CrossRef]
26. Braaten TJ, Brahmer JR, Forde PM, et al. Immune checkpoint inhibitor-induced inflammatory arthritis persists after immunotherapy cessation. *Ann Rheum Dis*. 2020;79(3):332-338. [CrossRef]
27. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf
28. Kostine M, Finckh A, Bingham CO, et al. EULAR points to consider for the diagnosis and management of rheumatic immune-related adverse events due to cancer immunotherapy with checkpoint inhibitors. *Ann Rheum Dis*. 2021;80(1):36-48. [CrossRef]
29. Gao J, Miao J, Sun H, et al. TNF-alpha inhibitor ameliorates immune-related arthritis and pneumonitis in humanized mice. *Front Immunol*. 2022;13:955812. [CrossRef]
30. Sørensen AS, Andersen MN, Juul-Madsen K, et al. Tumor necrosis factor alpha neutralization attenuates immune checkpoint inhibitor-induced activation of intermediate monocytes in synovial fluid mononuclear cells from patients with inflammatory arthritis. *Arthritis Res Ther*. 2022;24(1):43. [CrossRef]
31. Benesova K, Kraus FV, Carvalho RA, et al. Distinct immune-effector and metabolic profile of CD8(+) T cells in patients with autoimmune polyarthritis induced by therapy with immune checkpoint inhibitors. *Ann Rheum Dis*. 2022;81(12):1730-1741. [CrossRef]
32. Draghi A, Borch TH, Radic HD, et al. Differential effects of corticosteroids and anti-TNF on tumor-specific immune responses: implications for the management of irAEs. *Int J Cancer*. 2019;145(5):1408-1413. [CrossRef]
33. Leipe J, Mariette X. Management of rheumatic complications of ICI therapy: a rheumatology viewpoint. *Rheumatol (Oxf Engl)*. 2019;58 (suppl 7):vii49-vii58. [CrossRef]
34. Leipe J, Christ LA, Arnoldi AP, et al. Characteristics and treatment of new-onset arthritis after checkpoint inhibitor therapy. *RMD Open*. 2018; 4(2):e000714. [CrossRef]
35. Roberts J, Smylie M, Walker J, et al. Hydroxychloroquine is a safe and effective steroid-sparing agent for immune checkpoint inhibitor-induced inflammatory arthritis. *Clin Rheumatol*. 2019;38(5):1513-1519. [CrossRef]
36. Faje AT, Lawrence D, Flaherty K, et al. High-dose glucocorticoids for the treatment of ipilimumab-induced hypophysitis is associated with reduced survival in patients with melanoma. *Cancer*. 2018;124(18):3706-3714. [CrossRef]
37. Montfort A, Filleron T, Virazels M, et al. Combining nivolumab and ipilimumab with infliximab or certolizumab in patients with advanced melanoma: first results of a phase Ib clinical trial. *Clin Cancer Res*. 2021;27(4):1037-1047. [CrossRef]
38. De La Fuente F, Belkhir R, Henry J, et al. Use of a bDMARD or tsDMARD for the management of inflammatory arthritis under checkpoint inhibitors: an observational study. *RMD Open*. 2022;8(2) [CrossRef]
39. Kim ST, Tayar J, Trinh VA, et al. Successful treatment of arthritis induced by checkpoint inhibitors with tocilizumab: a case series. *Ann Rheum Dis*. 2017;76(12):2061-2064. [CrossRef]
40. Stroud CR, Hegde A, Cherry C, et al. Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade. *J Oncol Pharm Pract*. 2019;25(3):551-557. [CrossRef]
41. Bass AR, Abdel-Wahab N, Reid PD, et al. Comparative safety and effectiveness of TNF inhibitors, IL6 inhibitors and methotrexate for the treatment of immune checkpoint inhibitor-associated arthritis. *Ann Rheum Dis*. 2023; 82(7):920-926. [CrossRef]
42. Holmstroem RB, Nielsen OH, Jacobsen S, et al. COLAR: open-label clinical study of IL-6 blockade with tocilizumab for the treatment of immune checkpoint inhibitor-induced colitis and arthritis. *J Immunother Cancer*. 2022;10(9) [CrossRef]
43. Ma VT, Lao CD, Fecher LA, Schiopu E. Successful use of secukinumab in two melanoma patients with immune checkpoint inhibitor-induced inflammatory arthropathy. *Immunotherapy*. 2022;14(8):593-598. [CrossRef]
44. Leonardi GC, Gainor JF, Altan M, et al. Safety of programmed Death-1 pathway inhibitors among patients with non-small-cell lung cancer and preexisting autoimmune disorders. *J Clin Oncol*. 2018;36(19):1905-1912. [CrossRef]
45. Haanen J, Ernstoff MS, Wang Y, et al. Autoimmune diseases and immune-checkpoint inhibitors for cancer therapy: review of the literature and personalized risk-based prevention strategy. *Ann Oncol*. 2020;31(6):724-744. [CrossRef]
46. Magnusson MK, Dahlén R, Strid H, et al. CD25 and TNF receptor II reflect early primary response to infliximab therapy in patients with ulcerative colitis. *United Eur Gastroenterol J*. 2013;1(6):467-476. [CrossRef]
47. Magnusson MK, Strid H, Isaksson S, et al. Cultured blood T-cell responses predict anti-TNF therapy response in patients with ulcerative colitis. *Aliment Pharmacol Ther*. 2015;41(11):1149-1161. [CrossRef]
48. Gertel S, Polachek A, Furer V, et al. T cell functions of psoriatic arthritis patients are regulated differently by TNF, IL-17A and IL-6 receptor blockades in vitro. *Clin Exp Rheumatol*. 2022; 40(1):120-128. [CrossRef]
49. Gertel S, Polachek A, Furer V, et al. Synovial monocytes from psoriatic and rheumatoid arthritis patients are modulated differently by TNF inhibitors and glucocorticoids: an ex-vivo study. *Clin Exp Rheumatol*. 2023;41(9):1847-1855. [CrossRef]