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Original article

Autoantibody positivity predicts severity of rheumatic immune-related adverse events to immune-checkpoint inhibitors

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A B S T R A C T

Objective: Immune-related adverse events (irAEs) due to immune checkpoint inhibitors are responsible for a considerable burden of morbidity and mortality. Predictors of severity of rheumatic irAEs have not been identified yet. The objective of this study was to test the hypothesis whether the presence of autoantibodies could be associated with a more severe and difficult-to-treat clinical phenotype of rheumatic irAEs.

Methods: Patients referred to our centre due to the onset of rheumatic irAEs were prospectively recruited between June 2018 and December 2020. A pre-specified panel of autoantibodies was tested in each patient at baseline visit. All patients were started on glucocorticoids and then followed-up. Conventional or biologic immunosuppressants were started in case of steroid-refractory or relapsing disease. Logistic regression analysis was performed to evaluate the association between the baseline positivity of at least one autoantibody and the necessity of an add-on therapy.

Results: Fourty-three patients with rheumatic irAEs were enrolled. Twenty-five (58%) patients had positivity of at least one of the tested autoantibodies. Twenty-two (51%) patients required the start of an additional immunosuppressant during follow-up. The only factor associated with the necessity of an add-on therapy was autoantibody positivity (OR=9.65, 95% CI:2.09–44.56; *p-value* 0.004).

Conclusions: The presence of autoantibodies in patients with cancer who develop rheumatic irAEs could predict their progression to difficult-to-treat clinical manifestations. This finding might prompt a future therapeutic approach based on a tailored and earlier immunosuppressive treatment in selected cases.

1. Introduction

In the last decade, immune checkpoint inhibitors (ICIs) have become a therapeutic tool of paramount importance when managing malignancies. ICIs currently represent the standard of care for several advanced cancers [1]. Despite their remarkable efficacy, these agents are associated with the onset of peculiar clinical manifestations called immune-related adverse events (irAEs) [2].

Available guidelines recommend glucocorticoids as a first-line treatment to manage irAEs, whereas immunosuppressants should be administered in refractory and severe cases [3].

Little is known about factors that can influence the development and severity of irAEs following the administration of ICIs. Intriguingly, an association between humoral immunity and irAEs has been found in this regard. The presence of autoantibodies prior to the start of ICI increases the risk of developing irAEs [4] and may predict the severity of non-rheumatic manifestations [5].

Though the association between autoantibodies and rheumatic irAEs is not yet fully understood, these circulating biomarkers may be useful in identifying patients who are more likely to develop severe and refractory clinical manifestations. This approach could lead to an early start of immunosuppressants in addition to glucocorticoids and possibly guarantee a better control of clinical manifestations, along with a reduction in morbidity, mortality, and health-related costs [5].

The objective of this study was to determine whether the presence of autoantibodies in ICI-treated patients correlates with the severity and

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treatment refractoriness of rheumatic irAEs.

2. Methods

2.1. Study design and population

All patients with cancer referred to our Immune-related Adverse Event Clinic at San Raffaele Hospital were consecutively screened for eligibility between June 2018 and December 2020.

All patients had received treatment with at least one ICI targeting PD-1 (pembrolizumab, nivolumab), PD-L1 (atezolizumab, durvalumab), or CTLA-4 (ipilimumab) as part of routine clinical care for cancer treatment. Only patients with rheumatic irAE (i.e., arthritis, polymyalgia rheumatica [PMR]-like syndrome, vasculitis [involving skin or large vessels], myositis with or without concomitant myocarditis), >18 years of age and with no history of rheumatic disease prior to ICI treatment start were enrolled in the study. The diagnosis of rheumatic irAE was based on clinical examination and medical history; in case of suspected vascular, myocardial or muscle involvement, additional studies were performed. The diagnostic algorithm for each irAE is described in detail in the *Supplementary Material S1*.

The study was approved by the San Raffaele Ethics Committee (approval number DSAN854-A-OS/1). All patients gave written informed consent.

2.2. Baseline evaluation

At the first visit at our Clinic, information about previous oncologic history, ICI therapy and irAEs features was collected. Along with a thorough clinical evaluation, a pre-specified autoantibody blood panel was tested. This panel was performed in all cases in the laboratory of our hospital, and included the following: rheumatoid factor, anti-nuclear (ANA), anti-neutrophil cytoplasmic (ANCA), anti–citrullinated protein (ACPA), anti-dsDNA, anti-SSA/Ro 52, anti-SSA/Ro 60, anti-SSB, anti-Sm, anti-RNP, anti-Jo1, anti-heart (AHA), anti-b2-glycoprotein-I, anti-cardiolipin, anti-thyroid peroxidase (ATPO) and anti-thyroglobulin antibodies (ATG).

2.3. Treatment initiation and follow-up

At diagnosis, all patients were started on glucocorticoids, as recommended by available guidelines [3,6]. A starting dose of prednisone 0.5 mg/kg was administered to patients with arthritis, PMR-like syndrome, and cutaneous vasculitis. Higher-doses (i.e., 1 mg/kg) of steroids were given to patients with myositis and large vessel vasculitis. According to the specific irAE, starting treatment could also include intravenous immunoglobulins, hydroxychloroquine, or colchicine.

Patients underwent a monthly follow-up after treatment start. Disease activity of irAEs was re-assessed at each visit, both clinically and with the appropriate blood tests and imaging studies. Rheumatic clinical manifestations were accordingly defined as being either remitting or active, with a further distinction between low and high disease activity.

Immunosuppressive therapies were added either in case of primary unresponsiveness to glucocorticoids or relapse during steroids' tapering while patients were still on daily prednisone doses greater than 12.5 mg. Add-on therapies included conventional immunosuppressants (i.e., methotrexate and mycophenolate mofetil), biologic agents (i.e., tocilizumab, anakinra and rituximab) and intravenous immunoglobulins.

The protocol of treatment and monitoring for each irAE is described in detail in the *Supplementary Material S1*.

2.4. Statistical analysis

The primary endpoint of our study was to evaluate whether the baseline presence of autoantibodies was associated with the severity of rheumatic irAE. Given the heterogeneity of these manifestations, severity was defined as the need for additional immunosuppressive therapies during follow-up. Features of patients who required treatment escalation were compared to those who did not. Continuous and categorical variables were compared using independent samples Mann-Whitney U test and Fisher's exact test, respectively. Variables that differed (*p-value*<0.1) among the two subgroups were then included in a logistic regression analysis to predict the need for add-on therapies. Baseline positivity of at least one autoantibody was *a priori* included as a covariate.

We also specifically studied the influence of the most common types of irAEs in our cohort (i.e., arthritis, PMR-like syndrome, and myositis) and the history of a non-rheumatological irAEs on the outcome with a dedicated regression analysis.

Two separate analyses to evaluate possible predictors for add-on therapy in the sub-groups of patients treated with either a conventional immunosuppressant or a biologic agent were then performed.

A further sub-analysis was deemed necessary to mitigate the possible bias due to the known association between organ-specific antibodies and specific autoimmune diseases. This link – if statistically relevant in our cohort – might impact the analysis and lead to an overestimation of the predictive role of autoantibody positivity. The following associations were thus studied with Fisher's exact test: ATPO/ATG and thyroiditis, anti-Jo1 and myositis, AHA and myocarditis, ANCA and vasculitis. ACPA and arthritis were not evaluated as these antibodies were detected in none of our patients. In case of an identified association between a circulating antibody and a specific irAE, those patients were excluded from logistic regression.

Analyses were performed using statistical package SPSS 27.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Baseline evaluation

At the end of the study period (December 2021), 43 patients had been enrolled in the study and were included in the analysis. Their demographic and clinical characteristics are shown in Table 1. Lung cancer was the most common oncologic diagnosis, and all patients received an inhibitor of PD1 or PDL1. Median time between the initiation of ICI and the onset of irAEs was 2 (IQR 1–4) months. None of the patients had a personal rheumatologic history, and none had been tested for any of the autoantibody included in our panel before the start of ICIs.

As shown in Fig. 1A, arthritis was the most common irAE in our cohort. Ten (2%) patients experienced two or more concomitant rheumatic irAEs. In addition, five (12%) patients were diagnosed with thyroiditis, three (7%) with colitis, two (5%) with pneumonitis, one (2%) with hepatitis, and one (2%) with vitiligo. In most cases (8 [67%]), non-rheumatic irAEs preceded the rheumatic ones.

Twenty-five (58%) patients had baseline positivity of at least one of the tested autoantibodies; their relative frequencies are shown in Fig. 1B, with ANA being the most prevalent ones (40%). Three (7%) patients had two different autoantibodies and two (5%) patients had three. Anti-heart antibodies were significantly more prevalent in patients with myocarditis (*p-value* = 0.006). There was no association between ATPO/ATG and thyroiditis (*p-value* = 0.402), anti-Jo1 and myositis (*p-value*=0.296), ANCA and vasculitis (*p-value* = 0.370).

ICI, immune checkpoint inhibitors; irAEs, immune-related adverse events; PD-L1, programmed death ligand 1; PMR; polymyalgia rheumatica.

PMR, polymyalgia rheumatica.

3.2. Treatment and follow-up

Median starting dosage of glucocorticoids was 25 (IQR, 15–37.5) mg per day. Induction therapy included hydroxychloroquine in three patients; intravenous immunoglobulins and colchicine were started along

Table 1
Comparison of demographic and disease features between patients who received and patients who did not receive immunosuppressive treatments. Continuous and categorical variables are reported as median (interquartile range) and absolute frequency (percentage), respectively.

Variables	All patients ($n = 43$)	Patients requiring additional therapy ($n = 22$)	Patients not requiring additional therapy ($n = 21$)	*p-value*
Age (years)	73 (65 – 76)	68 (57 – 76)	74 (68–75)	0.436
Male sex	32 (74%)	16 (73%)	16 (76%)	1.000
Lung cancer	34 (79%)	17 (77%)	17 (81%)	1.000
Urothelial cancer	4 (9%)	2 (9%)	2 (9%)	1.000
Melanoma	5 (12%)	3 (14%)	2 ((9%)	0.604
Pembrolizumab	25 (58%)	10 (46%)	15 (71%)	0.124
Atezolizumab	3 (7%)	1 (5%)	2 (9%)	0.607
Nivolumab	13 (30%)	10 (46%)	3 (14%)	**0.045**
Durvalumab	2 (5%)	1 (5%)	1 (5%)	1.000
High PD-L1 expression *	5 (12%)	3 (14%)	2 (9%)	0.604
Delay from ICI to irAE (months)	2 (1 – 4)	4 (1 – 13)	6 (1 – 7)	0.778
Arthritis	31 (72%)	17 (77%)	14 (67%)	0.610
PMR-like syndrome	8 (19%)	4 (18%)	4 (19%)	1.000
Myositis	6 (14%)	4 (18%)	2 (9%)	0.279
with myocarditis	3 (7%)	2 (9%)	1 (5%)	0.270
Vasculitis	6 (14%)	3 (14%)	3 (14%)	1.000
Non-rheumatic irAEs	12 (28%)	7 (32%)	5 (24%)	0.446
Glucocorticoid dosage (mg per day)	25 (15 – 37.5)	25 (17.5 – 40)	25 (12.5 – 25)	0.279
Autoantibody positivity	25 (58%)	18 (82%)	7 (33%)	**0.002**
Anti-nuclear antibody positivity	17 (40%)	12 (55%)	5 (24%)	0.069
Anti-thyroid antibodies	5 (12%)	3 (14%)	2 (10%9	0.674
Oncological response to ICI	28 (65%)	14 (64%)	14 (67%)	0.525

* PD-L1 expression > 50%.

with steroids in two patients each.

The median follow-up duration was 6 (IQR, 2–13) months. During this interval, at least one add-on immunosuppressive drug was required in 22 (51%) patients. More specifically, in 13 (59%) patients immunosuppressive therapies were started because of primary steroid-resistance, whereas in 9 (41%) cases they were introduced following a relapse during tapering of glucocorticoids. In the latter group – as stated in the *Methods* section – the daily prednisone dose was always greater 12.5 mg when immunosuppressants were started.

Methotrexate was the most used conventional immunosuppressant (16 [37%] patients), whereas mycophenolate mofetil was administered to three (7%) patients. Tocilizumab was administered to five (12%) patients, while intravenous immunoglobulins and anakinra to three (7%) patients each. Only one (2%) patient was treated with rituximab.

In steroid-resistant patients, the start of immunosuppressants led to remission or low disease activity in 14 (64%) cases. This was paralleled by a significant reduction in the median daily dose of prednisone (from 22.5 [IQR,10–25] to 7.5 [IQR,5–10] mg per day; *p-value* < 0.001).

During the study period, six (14%) patients died. Five (83%) of them had tested positive for at least one autoantibody. Infection was the most frequent cause of death (four patients). The other two patients' deaths were caused by cancer progression and myositis-associated rhabdomyolysis, respectively.

3.3. Predictors of severity of immune-related adverse events

Differential features of patients who required an additional conventional or biologic immunosuppressive treatment and those who did not are shown in Table 1. Positivity of at least one autoantibody and use of nivolumab were more frequent in patients who received add-on therapies. According to the *Methods*, these two covariates were included in the logistic regression analysis. The presence of autoantibodies was the only factor significantly associated with the start of an immunosuppressant during follow-up (Odds Ratio [OR] 8.33, 95% Confidence Interval [CI] 1.83 –37.98; *p-value* = 0.006).

A dedicated logistic regression model showed that neither the type of rheumatic irAE (*p-value* = 0.991) nor an additional non-rheumatic irAE (*p-value* = 0.372) influenced the likelihood of requiring an immunosuppressant.

Dedicated sub-analyses in the sub-groups of patients treated with either a conventional immunosuppressant or a biologic agent showed that, in both cases, the association with autoantibodies' positivity remained significant (OR 6.22, 95% CI 1.56 - 24.71, *p-value*=0.009 and OR 5.93, 95% CI 1.46 – 24.09, *p-value* = 0.013, respectively).

After patients with myocarditis and/or AHA positivity were – according to *Methods* – excluded from the analysis, logistic regression confirmed a significant association between antibody positivity and the requirement of an immunosuppressant (OR 8.56, 95% CI 2.50 - 50.08, *p-value* = 0.002).

4. Discussion

To our knowledge, our study is the first to show that the presence of autoantibodies in patients who develop rheumatic irAEs predicts a higher necessity for immunosuppressants beside steroid therapy. This feature therefore identifies a population at greater risk of progressing to more severe manifestations. Such predictor could greatly impact clinical practice as it could prompt the early start of add-on therapies, thus possibly preventing the accrual of organ damage. In fact, irAEs are associated with remarkable morbidity and mortality, as well as significant costs [7] that could be reduced with a timely start of second-line therapies.

The importance of humoral autoimmunity in ICI-treated patients has been previously shown in a few studies. Both Toi and Gowen [4,5] have found that autoantibody positivity prior to the start of ICI is associated with the subsequent development of irAEs. While Toi et al. tested autoantibodies commonly used in clinical practice (e.g., ANA and anti-thyroid antibodies) [4], Gowen et al. performed an extended proteomic microarray evaluating over 19,000 autoantigens and showed an association between autoantibody positivity and the severity of non-rheumatic irAEs [5]. This finding is in line with our results, though Gowen et al. did not include information in regard to the refractoriness to treatment in their patients.

However, the relationship between humoral immunity and irAEs is not univocal. In their study, Ghosh et al. tested patients with a microarray panel prior to the start of ICI and then six weeks later. Surprisingly, patients who developed irAE had lower baseline concentrations of autoantibodies. Nonetheless, ICI-related autoimmune manifestations were associated with a significant increase in autoantibodies titers following the start of immunotherapy [8]. Accordingly, de Moel et al. studied a large population of patients affected by irAEs and found that almost 20% of them developed new autoantibodies following the start of ICI therapy. A positive association was found between seroconversion and the onset of irAEs [9]. These findings suggest the possibility of an ICI-induced antibody production in patients who develop irAEs. Indeed, this hypothesis is supported by the activating changes in circulating B-cells observed in ICI-treated patients by Das et al. [10]. Interestingly, this group also found that an early increase in peripheral plasmablasts is associated with a higher frequency of more severe irAEs.

In regard to the antigen-specificity, ANA were the most prevalent

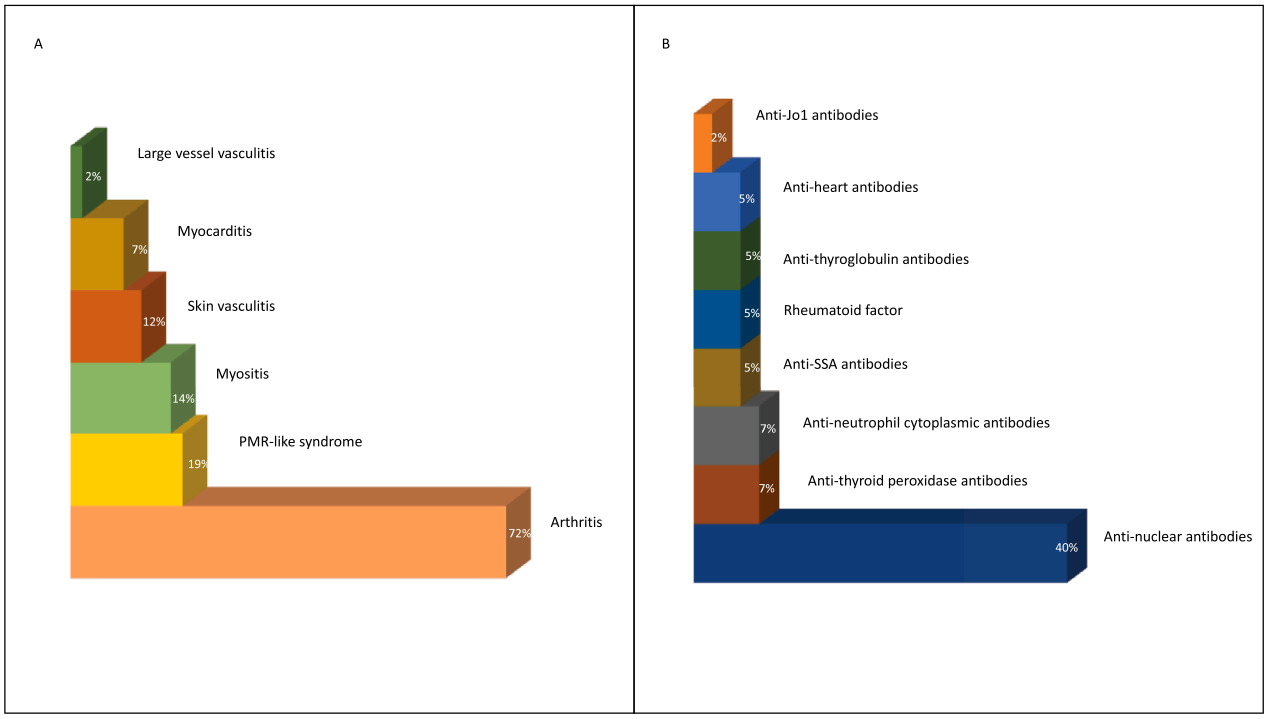

Fig. 1. Relative frequencies of different rheumatic immune-related adverse events (**panel A**) and autoantibodies (**panel B**) in our study population.

(50%) autoantibody in our study population. However, Head et al. previously reported positivity of these antibodies to be less frequent in patients affected by irAEs (27%) [11]. The difference of prevalence between these two cohorts might be explained by the fact that our patients were all affected by rheumatic irAEs, unlike those described in the previous study. Antigen-specificity has been previously shown to influence the development of specific irAEs. Kimbara et al. found that positivity of anti-thyroid antibodies predicted the development of ICI-related thyroiditis [12]. Interestingly, we did not find such an association in our cohort, while we found a higher prevalence of AHA in patients who developed ICI-related myocarditis. Though it is known that these autoantibodies are frequently found in patients with myocarditis [13], this is – to our knowledge – the first time such an association has been shown in ICI-induced inflammatory cardiomyopathy.

Indeed, while autoantibodies may represent a useful prognostic tool in the evaluation of patients with irAEs, it is known that such manifestations may be self-limiting in some cases [3]. Hence, a follow-up longer than that of our study (i.e., median of six months) is necessary to further confirm that these biomarkers are associated with persistent, severe activity of irAEs.

Intriguingly, no other factor was significantly associated with disease severity in our study population. While a high tumor expression of PD-L1 has been shown to predict the onset of irAEs [14], we did not find a correlation between this feature and severity of clinical manifestations in our cohort. Likewise, while a previous study found that non-lung cancers are more strongly associated with the onset of irAEs [1], in our study cancer histology did not influence the requirement for immunosuppressants.

Our findings also confirmed previous reports [3] regarding the effectiveness of immunosuppressants in the treatment of difficult-to-treat irAEs. In our cohort, these agents led to an optimal disease control in most of our patients. Moreover, immunosuppressive agents allowed a significant reduction in the dose of glucocorticoids. This is an important achievement since glucocorticoids have been shown to decrease the killing ability of cancer-infiltrating lymphocytes and may possibly worsen oncologic prognosis if administered chronically at moderate or high doses [3].

We acknowledge that our study has some limitations.

First, our study cohort included a lower number of patients compared to previous studies. Nonetheless, the prospective nature of the study and the rigorous regression model that was applied might have counterbalanced this limitation.

Second, none of our patients was tested for the presence of autoantibodies prior to the start of ICI therapy. However, even if autoantibodies were already present, their association with a more severe subset of disease would regardless be of interest as a predictive factor in clinical practice.

Third, we grouped together irAEs with different pathogenesis and manifestations, some of which are known to be associated with specific autoantibodies (e.g., myocarditis and myositis). Furthermore, some patients had concomitant non-rheumatic irAEs with an established link with serological markers (e.g., thyroiditis). Theoretically, these pathogenic associations might have impacted our analysis and may limit the interpretation of our findings. However, we performed a dedicated analysis and showed that only myocarditis was significantly associated with specific antibodies in our cohort, and a logistic regression that excluded patients with anti-heart antibodies confirmed the predictive role of autoantibody positivity in our cohort.

Finally, we considered the administration of an add-on immunosuppressant as a surrogate of disease severity. This was necessary in light of the heterogeneity of different irAEs included in the study. Though our protocols of care for different irAEs might be subject to inter -disease and -individual variability, all decisions on patient management were made by the same experienced clinicians at the same referral center. Furthermore, while other factors may commonly lead to the introduction of immunosuppressive agents (e.g., intolerance to glucocorticoids), in all of our patients they were started due to glucocorticoid-resistance, either primary or during tapering while still on moderate doses of prednisone. Even if this is not a validated endpoint in the management of irAEs and may not be always appropriate, it is well recognized as an indication for treatment escalation according to current guidelines [3].

In conclusion, our study showed for the first time that positivity of autoantibodies in patients who develop irAEs following ICI therapy predicts the necessity of second-line immunosuppressive agents. Even

though clinical trials are mandatory to confirm our findings, a tailored approach relying on baseline testing for autoantibodies in ICI-treated patients might prompt an early administration of immunosuppressants in selected cases and thus reduce mortality and morbidity related to irAEs.

Declaration of Competing Interest

The Authors declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.07.005.

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