The impact of two different rituximab-based strategies in cryoglobulinaemic vasculitis secondary to Sjögren's disease: a monocentric cohort study

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Abstract

Objective

To compare two different rituximab (RTX)-based therapeutic approaches on vasculitic and lymphoproliferative-related disease activity and on non-Hodgkin lymphoma (NHL) development in a cohort of patients affected by cryoglobulinaemic vasculitis secondary to Sjögren's disease (Sjögren-CryoVasc).

Methods

Three Sjögren-CryoVasc treatment groups were identified: 1) early RTX induction followed by maintenance; 2) late RTX induction with possible on-demand retreatment; 3) no RTX treatment. The following outcomes were evaluated: a) changes in cumulative ESSDAI, considering vasculitic-related and lymphoproliferative-related domains and changes in ESSDAI specific to each single vasculitic-related and lymphoproliferative-related domain; b) development of NHL; c) occurrence of persistent hypogammaglobulinemia associated with serious infections.

Results

13 Sjögren-CryoVasc patients were identified: 1) 5/13 treated earlier with RTX with subsequent maintenance; 2) 5/13 treated late with RTX with possible on-demand retreatment; 3) 3/13 not treated with RTX. The two RTX groups showed a decrease in the ESSDAI score with group 1 showing the most substantial reduction (p=0.028). Patients receiving RTX exhibited significant improvement in cutaneous, PNS, and articular vasculitic-related ESSDAI domains (p=0.007; p=0.006; p=0.03, respectively). By contrast RTX did not greatly affect the lymphoproliferative-related ESSDAI domains, even if an improvement was noted in the glandular and nodal domains for group 1 (p=0.03; p=0.03, respectively). No differences in NHL occurrence or safety concerns were observed between the groups.

Conclusion

RTX is an effective and safe treatment to control Sjögren-CryoVasc disease activity with a greater impact when administered earlier with a maintenance regimen. RTX alone cannot, however, affect the possible evolution of Sjögren-CryoVasc into an overt NHL.

Key words

Sjögren's disease, cryoglobulins, vasculitis, inflammation, non-Hodgkin lymphoma, rituximab, B-lymphocytes

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Received on March 2, 2024; accepted in revised form on April 11, 2024.

Competing interests: none declared.

Introduction

Cryoglobulinaemic vasculitis in Sjögren's disease (Sjögren-CryoVasc) represents a specific clinical phenotype characterised by B-cell lymphoproliferation and systemic inflammation, expressed as an immunocomplex-mediated vasculitis affecting the small vessels of the skin, nerves, joints, and occasionally the kidneys (1). CryoVasc prevalence among Sjögren's disease (SjD) patients is estimated around 3% and is associated with high disease activity, increased morbidity, and mortality (1, 2). The biological basis linking CryoVasc and SjD lies in the pronounced B-cell activation and the subsequent salivary MALT lymphoproliferation, which confers a higher risk of progression to non-Hodgkin lymphoma (NHL) compared to SjD without CryoVasc (3, 4).

In the context of CryoVasc, rituximab (RTX) was effective in lymphoproliferation and associated vasculitic and non-vasculitic manifestations, becoming a cornerstone in the therapeutic armamentarium against this condition (5, 6). However, efficacy and safety of RTX in the specific Sjögren-CryoVasc subgroup remain inadequately understood. The aim of this study is to compare three different therapeutic approaches, two of them based on RTX, to CryoVasc in SjD, by retrospectively analysing the data from our cohort of patients.

Materials and methods

Patients with an active follow-up who met both ACR/EULAR2016 classification criteria for SjD (7) and classification criteria for CryoVasc (8) were selected among all the patients with SjD followed from January to August 2023. Demographic, clinical and laboratory data were collected for each patient at the diagnosis of Sjögren-CryoVasc and at the last available assessment. Three groups based on the treatment approach were identified: 1) Early RTX induction with subsequent maintenance, defined as receiving either 250 mg/m^2 weekly x2 or 375 mg/m^2 weekly x4 within 6 months from Sjögren-CryoVasc diagnosis followed by a 6-month or annual maintenance regimen (500 mg or 1g) to ensure B-cell depletion (absence of peripheral CD19 B-cells); 2) Late RTX induction, defined as receiving either 250 mg/m^2 weekly x2 or 375 mg/m^2 weekly x4 more than 6 months from Sjögren-CryoVasc diagnosis, with on-demand retreatment, when clinically appropriate; 3) No RTX treatment. A retrospective evaluation from Sjögren-CryoVasc diagnosis (baseline) to the last assessment was conducted to examine: a) changes in disease activity, assessed by overall ESSDAI score considering CryoVasc manifestations (cutaneous, articular, peripheral nervous system, renal) and lymphoproliferative manifestations (glandular, nodal, biological, constitutional, pulmonary) and through each single ESSDAI domain related to the same manifestations; b) occurrence of NHL; c) presence of persistent hypogammaglobulinaemia, defined as gamma-globulin <8 g/L for at least 6 months, and hospitalisation or death due to infection. Lymphopenia and haematological ESSDAI domain were excluded due to the biological effect of RTX on lymphocyte count.

Ethics

This study was performed in accordance with the Declaration of Helsinki and was approved by CEUR-2017-Os-027-AS-UIUD, University of Udine, Italy.

Statistical analysis

Patients' demographic and clinical characteristics were presented with absolute values and percentages for categorical variables and medians (interquartile ranges [IQRs]) for continuous variables. The Kruskal-Wallis test and Fisher's exact test were employed to compare continuous and categorical variables among the three groups, respectively. Cochran-Armitage test was applied to assess any improvement trend in disease activity across the three groups. The significance level was set at $p<0.05$.

Results

Thirteen Sjögren-CryoVasc were identified among 372 SjD patients with an active follow-up. 10/13 patients were treated with RTX: 5 underwent early RTX induction with a subsequent fixed maintenance (group 1), and 5 received late RTX induction with on-demand re-

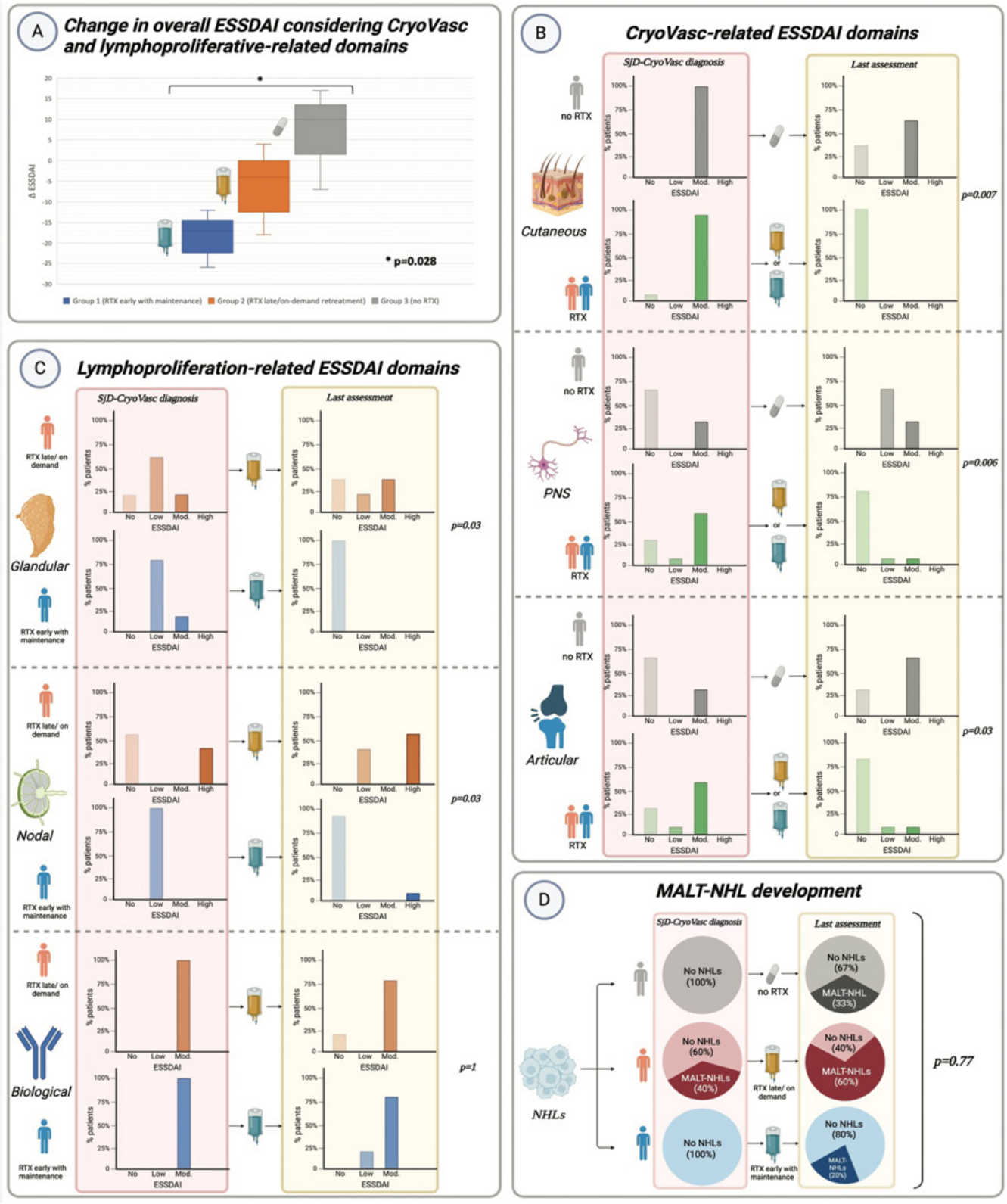

Fig 1. Main results.
A: Overall ESSDAI change considering CryoVasc-related (cutaneous, peripheral nervous system, articular, renal) and lymphoproliferative-related (constitutional, nodal, glandular, biological, pulmonary) domains.
B: Change in cutaneous, PNS and articular ESSDAI domains in patients treated with RTX (groups 1+2) vs no RTX (group 3).
C: Change in glandular, nodal and biological ESSDAI domains in patients treated with early RTX with maintenance (group 1) vs late RTX/on-demand retreatment (group 2).
D: MALT-NHLs development from Sjögren-CryoVasc diagnosis to the last assessment.
CryoVasc: cryoglobulinaemic vasculitis; RTX: rituximab; PNS: peripheral nervous system; NHL: non-Hodgkin lymphoma; MALT: mucosa-associated lymphoid tissue.

treatment (group 2). 3/13 were treated only with glucocorticoids, hydroxychloroquine, and colchicine (group 3) (Supplementary Fig. S1). Indications for RTX were clinical manifestations related to CryoVasc, including cutaneous, peripheral nervous system, and articular symptoms, except for two patients from group 2 who were treated based on haematological recommendation, stemming from a prior diagnosis of NHL. None of the patients receiving RTX were concurrently treated with steroids, colchicine, HCQ, or other immunosuppressive drugs. No differences were reported among the three groups at Sjögren-CryoVasc diagnosis, except for the higher frequency of low C4 and higher ESSDAI nodal domain score among the subjects treated with RTX (Suppl. Tables S1, S2).

Changes in disease activity according to single and overall ESSDAI domains

A notable decrease in overall ESSDAI from baseline to the last assessment, considering the domains related to CryoVasc and lymphoproliferative manifestations, was highlighted in the 2 groups receiving RTX compared to group 3. This reduction was much higher in group 1, which received early RTX induction with maintenance (median change: -17 *vs*. -4 *vs*. 10; H=7.12; p=0.028) (Fig. 1A).

Regarding the ESSDAI domains related to CryoVasc, a statistically significant improvement from baseline to the last assessment was recorded in the cutaneous, peripheral nervous system, and articular domains among patients undergoing RTX compared to those not undergoing RTX (p=0.007; p=0.006; p=0.03; respectively) (Fig. 1B). However, this difference was not observed between those receiving the two distinct RTX regimens (p=N/A; p=0.21; p=0.17, respectively) (Suppl. Fig. S2B). No renal involvement was recorded.

Furthermore, when considering glandular and nodal ESSDAI domains, no significant improvement was observed between those undergoing RTX and those not undergoing RTX (p=0.43; p=0.15, respectively) (Suppl. Fig. S2A). However, upon evaluating the two RTX schemes, an improvement in the glandular and nodal ESSDAI was noted in patients receiving early RTX induction with maintenance (p=0.03; p=0.03, respectively) (Fig. 1C). Notably, this difference was not found in biological ESSDAI domain either when comparing patients who received RTX with those who did not, nor between patients who received the two different RTX regimens (p=0.12; p=1, respectively) (Suppl. Fig. S2A, Fig. 1C].

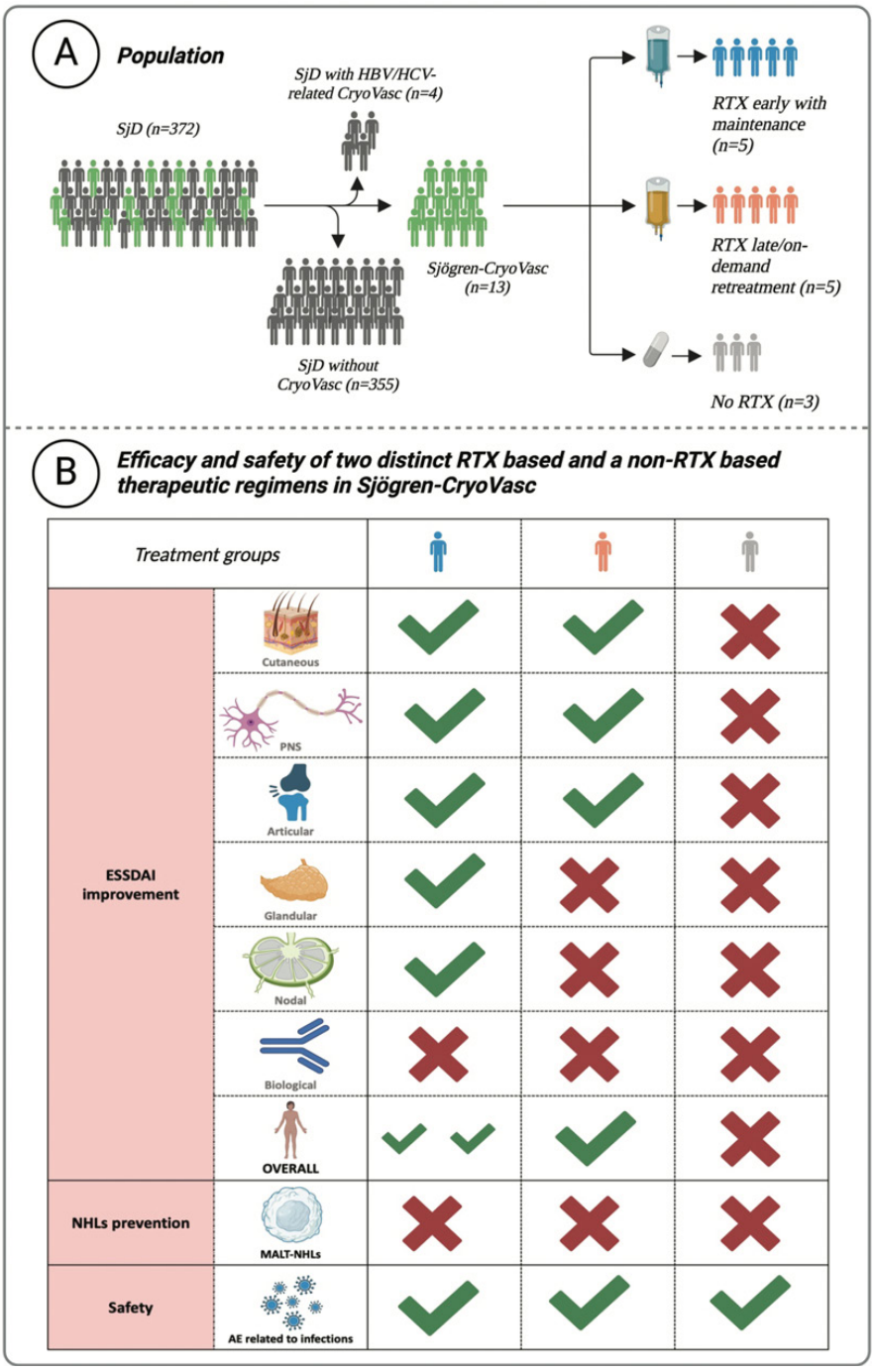

Fig. 2. The impact of two distinct Rituximab-based therapeutic regimens and non-RTX approach in Sjögren-CryoVasc. (**A**) Selection process of Sjögren-CryoVasc population. (**B**) Overview of efficacy in terms of overall and single ESSDAI domains improvement, as wells as prevention of NHLs, and safety related to infectious adverse events across three treatment regimens: 1) early RTX induction with subsequent maintenance; 2) late RTX induction with on-demand retreatment; 3) no RTX.
SjD: Sjögren's disease; CryoVasc: cryoglobulinemic vasculitis; Sjögren-CryoVasc: cryoglobulinaemic vasculitis secondary to Sjögren's disease; RTX: rituximab; PNS: peripheral nervous system; NHL: non-Hodgkin lymphoma; MALT: mucosa-associated lymphoid tissue; AE: adverse event.

Finally, regarding the constitutional domain, only one patient in group 1 presented fever, which regressed immediately after the first RTX. No pulmonary involvement was recorded.

NHL development

Two patients from group 2 developed MALT-NHLs before the onset of Sjögren-CryoVasc. At the time of the diagnosis of Sjögren-CryoVasc and during follow-up the persistence of lymphoma was still histologically evident in these two patients. MALT-NHL of new onset developed in three patients, one from each group, without any difference among the 3 groups (p=0.77) (Fig. 1D).

Persistent hypogammaglobulinaemia, infection-related hospitalisation and mortality

From the diagnosis of Sjögren-CryoVasc to the last follow-up, no major infectious adverse events requiring hospitalisation or resulting in death were recorded in any group. Persistent hypogammaglobulinaemia was noted only in a subject from group 1 and group 2 respectively (p=1).

Discussion

SjD is the autoimmune disease showing the highest frequency of B-cell NHL and cryoglobulinaemia (9, 10); these entities are closely linked through B-cell hyperactivation and dysregulation (4). RTX has been employed in clinical practice in both CryoVasc and SjD, yielding divergent outcomes. While proving effective in CryoVasc and establishing itself as a cornerstone treatment for this condition (6), RTX failed in SjD in the TRACTISS and TEARS trials, as well as on lymphoproliferative risk (11-14). However, no study has specifically explored the use of RTX in the Sjögren-CryoVasc subset; indeed, TEARS and TRACTISS did not perform a proper stratification of SjD patients, particularly overlooking the Sjögren-CryoVasc subgroup (12, 13). Our pilot study suggests that RTX-based regimens in Sjögren-CryoVasc may achieve a substantial long-term improvement in vasculitic and lymphoproliferative activity. Interestingly, a more aggressive B-cell depletion approach appears to enhance disease control compared to milder strategies, emphasising the role of anti-CD20 antibody in downregulating the cryoglobulin-producing B-cell clones in Sjögren-CryoVasc and therefore in controlling the lymphoproliferative manifestations over the medium-long period.

The separate assessment of the efficacy of two different RTX regimens on vasculitic and lymphoproliferative disease activity has also allowed us to outline two disease profiles that may alternatively benefit from different B-cell depleting strategies in the maintenance.

In Sjögren-CryoVasc, ESSDAI domains related to vasculitic-inflammatory manifestations showed a significantly greater trend of improvement in patients treated with RTX, regardless of the regimen used. On the contrary, considering ESSDAI domains related to lymphoproliferative manifestations, no significant difference was observed between patients treated and not treated with RTX; nevertheless, an improvement emerged when considering patients undergoing an intensive scheduled RTX maintenance compared to those with an on-demand approach; further stratification of Sjögren-CryoVasc patients is therefore necessary to determine the most effective therapeutic strategy. Notably, when considering only the biological ESSDAI, RTX fails to consistently improve the trend in this specific domain, highlighting the necessity of a treatment strategy focused on completely eradicating residual B-cell hyperactivity, both in peripheral blood and target tissues in SjD (14, 15). In this regard, RTX alone showed no preventive or significant therapeutic efficacy on the development of NHL in Sjögren-CryoVasc; however, the limited number of patients affected these results and does not allow to draw definite conclusion. Finally, encouragingly, no serious infections were recorded with any RTX regimen.

Our study has a few limitations: firstly, its retrospective design and the small number of patients in each group; secondly, the duration of follow-up which did not ever consistently prove homogeneous, as some subjects had a significantly shorter follow-up compared to others. Despite limitations, our study is a pioneering exploration of various RTX regimens in the Sjögren-CryoVasc subset, providing valuable insights and opening avenues for further research in this specific and rare clinical setting.

In conclusion, our retrospective study is the first evaluating the impact of two distinct RTX-based strategies on Sjögren-CryoVasc, which is becoming the most frequent CryoVasc in the era of hepatitis C virus worldwide eradication (16) (Fig. 2). Our results underscore RTX efficacy and safety in decreasing Sjögren-CryoVasc disease activity. Further B-cell targeted therapies aiming at improving pathogenic B-cell clone suppression are needed.

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