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Autoimmune Cytopenias in Rheumatic Disorders: Role of Rehabilitation in Functional Recovery

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Abstract: Rheumatic diseases are complicated by autoimmune cytopenias (ITP, AIHA, Evans syndrome), which are also closely related to fatigue and inferior functional status. Functional recovery and morbidity related to disease may be facilitated through rehabilitation programs in this population. The purpose of the study was to determine the impacts of a 12-month rehabilitation program during the period of July 2024- July 2025 on hematologic parameters, fatigue, and functional status, quality of life, and corticosteroid requirements in adults with autoimmune cytopenias in rheumatic disorders. A cross-sectional trial of 109 autoimmune cytopenias (ITP, AIHA, and Evans) patients who had a 12-month structured rehabilitation program. Control data involved demographic, rheumatic diagnosis, form of cytopenia, hematologic, concomitant immunosuppressive treatment, and functional/quality-of-life (Fatigue Severity Scale [FSS], Health Assessment Questionnaire [HAQ], SF-36 PCS/MCS, and 6-minute walk test [6 MWT]). The baseline data indicated that the majority of females (77.1%), as well as those with systemic lupus erythematosus, had the largest proportion of the most common rheumatic diagnosis (62.4%). Baseline revealed that a majority of patients were taking corticosteroids (89.9%), and co-therapies such as mycophenolate, azathioprine, and rituximab were prevalent. Six months later, the observed changes comprised positive changes in hemoglobin (9.8 + 1.9) to 11.9 + 1.6g/dL; platelet count (85.4 + 61.3) to 121.8 + 55.2 x 10 9/L; and corticosteroid dose (25.4 + 14.2) to 12.1 + 10.5mg/day. After the Functional/QOL FSS reduced to 4.1 ± 1.5 instead of 5.8 ± 1.1; HAQ rose to 1.1 ± 0.6 instead of 1.6 ± 0.7; SF-36 PCS scaled to 41.8 ± 9.1 instead of 32.5 ± 8.4; SF-36 MCS had a scale of 46.5 ± 9.3 instead of 39.2 ± 10.1, and 6MWT In general, the proportion of participants who told of meaningful changes in mobility (71.6%), fatigue (75.2%), daily activities (68.8%), as well as mood/well-being (65.1%), was high. The adherence to the programs was also high at 89.9 percent of the participants who completed the entire course, and 87.2 percent of the program participants said the program was well-tolerated. A 12-month follow-up rehabilitation program has been linked with clinically significant changes in hematologic condition, fatigue, functional capacity, and quality of life in patients with autoimmune cytopenias, complicating rheumatic diseases, and allowing the corticosteroid-sparing effects. Such determinants of functional improvement were baseline fatigue, adherence, and more focused optimization of therapy.

Keywords: Autoimmune cytopenias, hematological, and concomitant immunosuppressive therapies.

INTRODUCTION

A major clinical overlap that is between hematology and rheumatology involves autoimmune cytopenias, which are the immune-mediated destruction or production of erythrocytes, leukocytes, and thrombocytes [Tangye, S. G. *et al*., 2020]. These cytopenias are not merely laboratory abnormalities in the systemic immunity and rheumatological diseases, they can be the most essential signs of the disease activity, which has a serious influence on the prognosis of a patient, and is a critical step in determining the severity of therapy. In individuals with occasional rumbling repertoire of autoimmune cytopenias, one equates a rather broad collection of rheumatic disorders, including systemic lupus erythematosus (SLE), Sjogren syndrome, the autoimmune arthritis's, antiphospholipid syndrome (APS), and granulomatosis with polyangiitis (GPA). The clinical extend of autoimmune cytopenias in rheumatic disease is comprehensively capped off by several factors [Ottaviano, G. *et al*., 2020]. Firstly, cytopenias can be detected as a prelude or a negative portent of a deeper pathology exacerbation or global disease involvement and ought, therefore, to prompt urgent and vigorous re-evaluation of course action and organ damage [Hadjadj, J. *et al*., 2019]. Secondly, they can be a giant to the disease management by limiting the therapeutic toolkit of immunosuppressive agents, exposing patients to various opportunistic infections, or requiring supportive treatment, which can be transfusion, and specialized hematology consultation. The comorbidity between autoimmune cytopenias is in the majority of cases a predictor of a state of extreme immune dysregulation that will give important facts on the prognostication and the design of the long-term treatment measures. In experimental animals, the autoimmune cytopenias of rheumatic disorders are typically due to the generation of autoantibodies that bind lineage specific antigens further in the erythrocytes, platelets or neutrophils, thereafter, the clearance occurs through the processes of

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complement activation and by phagocytosis through the Fc-receptor [Speckmann, C. *et al*., 2017; Liston, A. *et al*., 2008; Farmer, J. R. *et al*., 2019]. In SLE e.g. the deposition of immune complexes and broad repertoire of autoantibodies, such as erythrocyte, platelet and phospholipid-antigen antibodies, has a direct role in hemolysis and thrombocytopenia where there is resultant compensatory reticulocytosis and unstable peripheral leukocyte response [Delmonte, O. M. *et al*., 2020]. Other rheumatic diseases often have a multifactorial etiology of cytopenias which is a mix of autoantibody mediated destruction, drug-related issues (e.g. with methotrexate, azathioprine, or biologic drugs), bone marrow suppression by chronic inflammation, and hypersplenism [Cifaldi, C. *et al*., 2022]. Consequently, the difference between the initial immune-mediated cytopenias and those that are secondary to the underlying disease process or its treatment is the crucial indicator to the intermediate work-ups of diagnosis and is what determines the remaining potential forms of management [Lechner, K., & Jäger, U. 2010; Neunert, C. 2011]. Genetically predisposed to autoimmune cytopenias, triggered by environments, and respond to the evolving environment of immunosuppressive therapies, epidemiologically there is much heterogeneity in the prevalence, severity, and individual trends of autoimmune cytopenias across occurrences across diverse rheumatic diseases and diverse ethnic groups [Ladogana, S. *et al*., 2016]. AIHA is a complication of SLE that has been adequately outlined and the manner in which it has impacted on patient morbidity and the quality of life cannot be underestimated. Neutropenia occurs less frequently, but it has a distinctive clinical issue because it increases the risk of developing infections and can complicate the antimicrobial stewardship and administration of immunosuppressive therapy to patients with underlying inflammatory disease. [Ladogana, S. *et al*., 2018]

METHODOLOGY

The study was implemented as a cross-sectional one based on the use of adults with autoimmune cytopenias (ITP, AIHA, or Evans syndrome) in the setting of rheumatic diseases to assess a 12-month rehabilitation study as an intervention tool in functional recovery. There were exclusion criteria like uncontrolled infection, active malignancy, severe organ dysfunction or contraindication to moderate intensity of aerobic and resistance training. Additional therapies that were identified as concomitant therapy comprised corticosteroid dose, immunosuppressants (mycophenolate mofetil, azathioprine, rituximab and cyclosporine) and IVIG. The rehabilitation intervention combined, supervised aerobic conditioning, resistance training, flexibility training, and fatigue-management, provided three times in a week and a duration of 12 months. Every session involved a warm-up, a period of 3045 minutes of aerobic exercise (treadmill walking or cycling) at moderate intensity (RPE 1214 on the Borg scale) and later, 20 – 30 minutes of resistance sports training of major muscle groups, and finally, a cool-down and stretching. The progression was individualized, as assessed by weekly measurement of effort tolerance and symptom burden, and altered in terms of intensity, duration and exercise modality when necessary. Functional/quality-of-life (FSS, HAQ, SF-36 PCS/MCS, 6MWT) and primary hematologic outcomes (hemoglobin, platelet count, and corticosteroid dose) were captured at the point of baseline and just after the rehabilitation. The functional and QoL tests were performed by blinded assessors as they aimed to reduce bias in the measurement. Data analyses were done by descriptive statistics to describe the characteristics at baseline and paired t-tests or other nonparametric counterparts were used to compare the values before and after rehabilitation. Multivariate linear regression was used to identify predictors of change in HAQ score (ΔHAQ) including covariates such as baseline hemoglobin and FSS, age, and rehabilitation adherence and corticosteroid-sparing effect. The statistical outcomes were settled by SPSS, version 24.0.

RESULTS

Table 1. Enroll demographic features of 109 patients in the patients.

Characteristic	Category	Number (n)	Percentage (%)
Sex	Male	25	22.9%
	Female	84	77.1%
Age (years)	18-30	19	17.4%
	31-50	47	43.1%
	51-65	36	33.0%

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	>65	7	6.4%
Rheumatic Diagnosis	Systemic Lupus Erythematosus (SLE)	68	62.4%
	Rheumatoid Arthritis (RA)	22	20.2%
	Sjögren's Syndrome	11	10.1%
	Other	8	7.3%

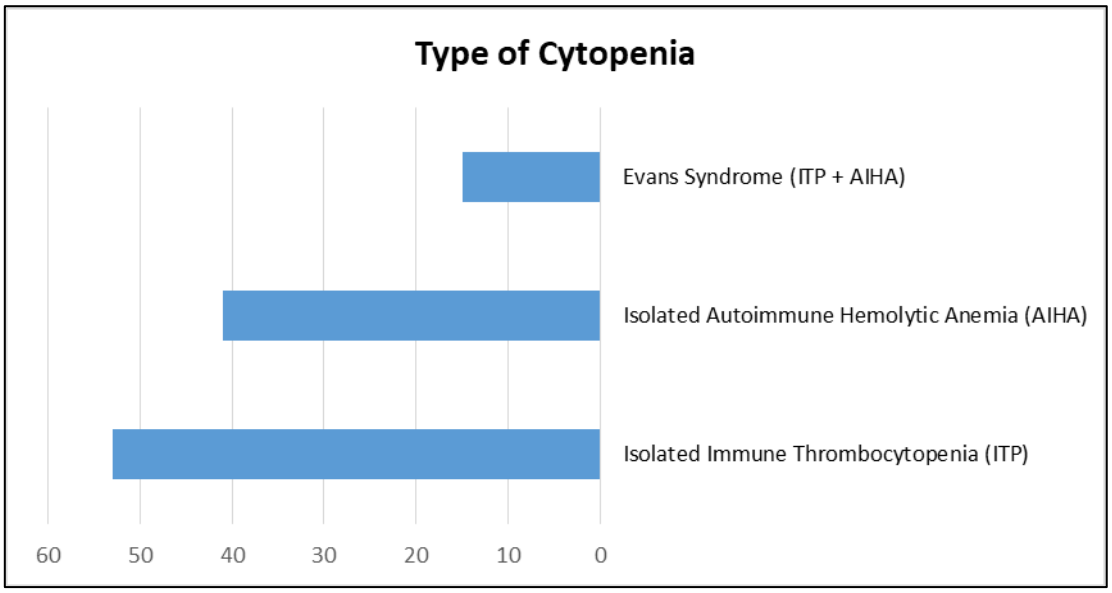

Figure 1: Distribution of the autoimmune cytopenia types during the diagnostic period.

Table 2: Identifying hematological data in this cross-sectional study.

Parameters	All Patients (N=109)	ITP Group (n=68)	AIHA Group (n=56)
Hemoglobin (g/dL)	9.8 ± 1.9	11.2 ± 1.5	8.1 ± 1.4
Platelet Count (x10⁹/L)	85.4 ± 61.3	52.7 ± 38.1	132.6 ± 58.9
Reticulocyte Count (%)	4.5 ± 2.8	2.1 ± 1.0	7.2 ± 2.5
Lactate Dehydrogenase (LDH) (U/L)	328 ± 155	265 ± 98	412 ± 168

Table 3: Classifying the therapies of concomitant immunosuppressive in the patients.

Medications	Number of Patients (n)	Percentage (%)
Corticosteroids	98	89.9%
The Prednisone of Equivalent Dose (mg/day)	(Mean ± SD: 25.4 ± 14.2)	
Mycophenolate Mofetil	45	41.3%
Azathioprine	32	29.4%
Rituximab	28	25.7%
Cyclosporine	15	13.8%
Intravenous Immunoglobulin (IVIG)	67	61.5%

Table 4: Assessment of functional outcomes of all participants in this study.

Assessment Tool	Score (Mean ± SD)	Possible Range
Fatigue Severity Scale (FSS)	5.8 ± 1.1	1-7 (Higher = worse)
Health Assessment Questionnaire (HAQ)	1.6 ± 0.7	0-3 (Higher = worse)
SF-36 Physical Component Summary (PCS)	32.5 ± 8.4	0-100 (Higher = better)
SF-36 Mental Component Summary (MCS)	39.2 ± 10.1	0-100 (Higher = better)
6-Minute Walk Test (6MWT, meters)	298 ± 105	N/A

Table 5: Determining clinical outcomes of hematological in post-12-month rehabilitation program.

Outcome	Pre-Rehab (Mean ± SD)	Post-Rehab (Mean ± SD)	p-value
Hemoglobin (g/dL)	9.8 ± 1.9	11.9 ± 1.6	<0.001
Platelet Count (x10⁹/L)	85.4 ± 61.3	121.8 ± 55.2	<0.001
Corticosteroid Dose (mg/day)	25.4 ± 14.2	12.1 ± 10.5	<0.001

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Table 6: Assessment of the post-rehabilitation program of health quality of life.

Assessment Tool	Pre-Rehab (Mean ± SD)	Post-Rehab (Mean ± SD)
Fatigue Severity Scale (FSS)	5.8 ± 1.1	4.1 ± 1.5
Health Assessment Questionnaire (HAQ)	1.6 ± 0.7	1.1 ± 0.6
SF-36 Physical Component Summary (PCS)	32.5 ± 8.4	41.8 ± 9.1
SF-36 Mental Component Summary (MCS)	39.2 ± 10.1	46.5 ± 9.3
6-Minute Walk Test (6MWT, meters)	298 ± 105	367 ± 96

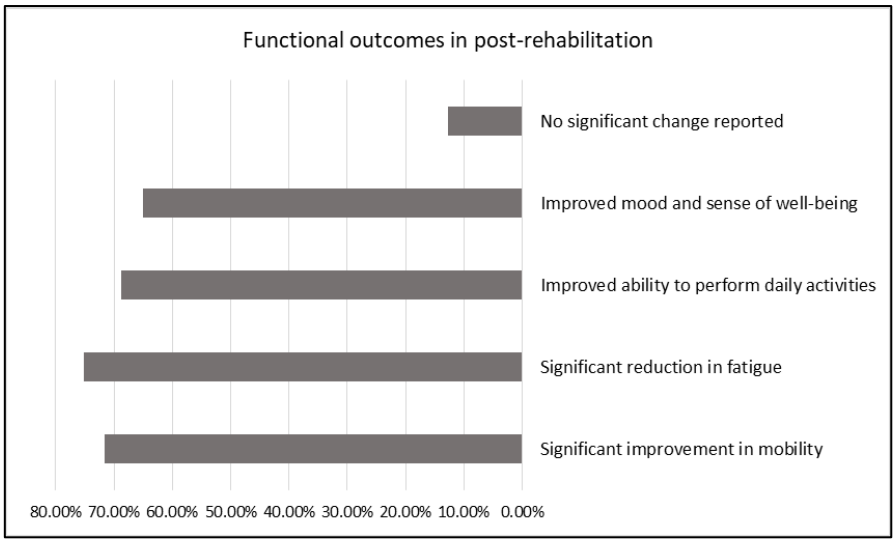

Figure 2: Assessment of the improvement outcomes which reported by patients in post-rehabilitation.

Table 7: Enroll clinical outcomes of patients in rehabilitation adherence.

Metric	Result
Completed a full 12-month program	98/109 (89.9%)
Withdrew due to disease flare	6/109 (5.5%)
Withdrew for personal/logistical reasons	5/109 (4.6%)
Assessed the program as tolerated as	95/109 (87.2%)
Required program modifications due to fatigue	34/109 (31.2%)

Table 8: Multivariate analysis in predication the affected factors on functional outcomes.

Predictor Variable	Beta Coefficient	95% Confidence Interval	p-value
Baseline Hemoglobin Level	-0.12	(-0.19 to -0.05)	0.001
Baseline Fatigue (FSS) Score	0.21	(0.10 to 0.32)	<0.001
Age	0.01	(0.00 to 0.02)	0.04
Adherence to Rehabilitation Sessions	-0.35	(-0.50 to -0.20)	<0.001
Reduction in Corticosteroid Dose	-0.09	(-0.15 to -0.03)	0.003

DISCUSSION

It was a mostly female cohort with a heavy weighted systemic lupus erythematosus with isolated immunological thrombocytopenia (ITP) and autoimmune hemolytic anemia (AIHA) being the predominant cytopenia subtypes. Clinically significant improvements associated with the incorporation of rehabilitation into the mainstream treatment implied that rehabilitation is potentially an effective intervention to add to the multidisciplinary approach to the treatment of this complex group of patients [Neunert, C. *et al*., 2019; Provan, D. *et al*., 2019]. The most noticeable results were the hematologic improvement and corticosteroid sparing. The reversal of hemoglobin was increased to 11.9 g/dL, and platelet counts to 121.8 x 10 9/L, which was highly significant ($p < 0.001$). Meanwhile, the mean dose of prednisone-equivalent decreased by 12.1mg/day. These paralleled improvements, even though causality cannot be conclusive using a non-randomized design, suggest a synergistic role of rehabilitation on disease activity and treatment burden. The observed steroid-sparing tendency is clinically significant, as it is not a secret that the prolonged corticosteroid exposure of rheumatic patients leads to numerous undesirable metabolic and infectious complications [Sipurzynski, J. *et al*., 2016].

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Durable improvements were also established in functional status and quality of life. Post 12 weeks, fatigue significantly decreased (FSS 5.8 to 4.1), and HAQ scores changed to 1.6 to 1.1, with significant changes indicating perceived changes in disability. The 6-minute walk test (6MWT) as an objective functional capacity improved by 298 meters to 367 meters, which highlights the improvements in the aerobic endurance. There was also an improvement in health-related quality of life, which was recorded by the use of the SF-36 components; there was an increase in the physical and mental health (PCS 32.5-41.8; MCS 39.2-46.5). The subjective measures coincide with the objective measures, and it is possible to conclude that the meaning of rehabilitation contributes to daily functioning and general well-being in this population group in a significant way [Auphan, N. *et al*., 1995; Hartung, H. P. 2008]. The full 12-month program was completed in 89.9 percent of subjects, and there was comparatively low dropout rates of the program because of disease exacerbation and personal factors. These results proved the fact that the rehabilitation is safe to be offered to patients with cytopenias on immunosuppressive therapy when properly adapted [Sève, P. *et al*., 2013]. The multivariate analysis showed that the strongest predictors of functional improvements were the baseline fatigue (FSS) and program adherence, with greater fatigue levels and adherence predicting greater functional improvements [Seidel, M. G. 2014]. There was also a small but significant association with baseline hemoglobin, which indicates that anemic patients can gain a significant amount of functional advantage of rehabilitation. Taper of the corticosteroid regime lead to gain of functions, implying that steroid saving may be coupled with functionality [Walter, J. E. *et al*., 2016; Seidel, M. G. 2020]. This combination of predictors suggests the patient-centered approach, in which patients with a higher level of fatigue, a stronger engagement in the program, and a higher metabolic reserve can record the most significant improvements [Leiding, J. W., & Forbes, L. R. 2019; Delmonte, O. M. *et al*., 2019; Miano, M. *et al*., 2015]. There are significant clinical implications of these findings. Structured rehabilitation as part of standard post-diagnosis care in autoimmune cytopenias of rheumatic diseases would potentially improve hematologic safety, minimize steroid intake, and improve physical functioning and QoL. Referral, especially to patients who have already developed substantial fatigue and functional impairment, might have the greatest benefits. [Koneti Rao, V. *et al*., 2005]

CONCLUSION

A 12-month instrumentalized rehabilitation in this sample of 109 rheumatic disease-related autoimmune cytopenias produced clinically significant improvements in blood cell counts, functional capacity, and quality of life with high adherence and excellent tolerability. It is important to note that Hg increased to 11.9 g/dL, and the number of platelets was 121.8 x109/L as compared to 85.4, and the corticosteroid exposure significantly reduced. There were also significant improvements in functional outcomes, decreases in fatigue and disability, and increases in 6MWT distance, and improvements in SF-36 scores. Multivariate analysis revealed that higher baseline fatigue, greater adherence, higher baseline hemoglobin, and corticosteroid taper were correlated with greater HAQ improvement, indicating that targeted rehabilitation, particularly in fatigued patients and combined with steroid-sparing plans, can be used to improve the functioning of these patients and lessen the burden of treatment in this group.

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