Successful Substitution of Prednisone by Saccharomyces cerevisiae in Immune Thrombocytopenic Purpura: First Documented Case of Beta-Glucan-Mediated Immunomodulation via GALT Pathway

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ABSTRACT

Background: Conventional treatment of Immune Thrombocytopenic Purpura (ITP) with corticosteroids presents significant adverse effects and variable efficacy. Beta-glucans from Saccharomyces cerevisiae demonstrate immunomodulatory properties in experimental autoimmune models, but clinical application in ITP remains unexplored.

Objective: Document the first case of successful corticosteroid substitution by S. cerevisiae in ITP, with comparative efficacy analysis and mechanistic hypothesis centered on gut-associated lymphoid tissue (GALT) modulation.

Case Presentation: A 30-year-old male with primary ITP (Hospital Erasto Gaertner, medical record 22004146) presented with nadir platelet count of 22,000/mm^3. Prednisone treatment achieved peak of 102,000/mm^3, followed by 51% decline during tapering (final: 50,000/mm^3). Following prednisone discontinuation, S. cerevisiae (2.5g/day oral capsules) was initiated. Within 15 days, platelets reached 127,000/mm^3 (24.5% superior to corticosteroid peak), with stable leukocytes (5,430-6,730/mm^3 vs 6,510-12,450/mm^3 with prednisone). Inadvertent dose omission resulted in 11.8% decrease vs 51% during prednisone tapering. Comprehensive metabolic evaluation demonstrated normal vitamin D3 (40.7 ng/mL), normal iron studies, normal hepatic/renal function. MCV (87.50 fL) and RDW (12.40%) excluded macrocytosis, ruling out B12/folate deficiency.

Discussion: Superior platelet response with preserved immune function (stable leukocytes, normal inflammatory markers) suggests selective immunomodulation via beta-glucan interaction with GALT receptors (Dectin-1, TLR-2), inducing regulatory T cells and tolerogenic dendritic cells. This mechanism fundamentally differs from prednisone's nonspecific immunosuppression, explaining superior efficacy without leukocyte variability. GALT-mediated peripheral tolerance may reduce anti-platelet autoantibody production and splenic phagocytosis.

Conclusion: This represents the first documentation of successful corticosteroid substitution by yeast beta-glucans in ITP, achieving superior platelet response through selective GALT-mediated immunomodulation. Randomized controlled trials are needed to confirm efficacy and elucidate mechanism via anti-platelet antibody quantification and Treg profiling.

Keywords: Immune Thrombocytopenic Purpura; Saccharomyces cerevisiae; Beta-glucans; GALT; Regulatory T cells; Immunomodulation; Prednisone alternative

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1. INTRODUCTION

1.1 Clinical Challenge of ITP Management

Immune Thrombocytopenic Purpura (ITP) affects approximately 3-4 per 100,000 adults annually, characterized by autoantibody-mediated platelet destruction, predominantly via anti-GPIIb/IIIa and anti-GPIb/IX antibodies [1]. Splenic macrophages and hepatic Kupffer cells phagocytose opsonized platelets, while bone marrow megakaryopoiesis is paradoxically suppressed by anti-platelet antibodies that cross-react with megakaryocyte surface antigens [2].

First-line treatment relies on corticosteroids (prednisone 1-2 mg/kg/day, dexamethasone 40 mg/day × 4 days), achieving initial response in 60-80% of patients [3]. However, sustained remission occurs in only 20-30%, necessitating prolonged therapy with consequent adverse effects: hyperglycemia, osteoporosis, weight gain, hypertension, and increased infection risk [4]. Rebound thrombocytopenia during tapering affects up to 50% of patients [5].

1.2 Beta-Glucans as Immunomodulators

Saccharomyces cerevisiae cell wall contains 50-60% beta-1,3/1,6-glucans, branched polysaccharides recognized by innate immunity pattern recognition receptors [6,7]. Unlike corticosteroid-mediated pan-immunosuppression, beta-glucans exert selective immunomodulation via:

1. Dectin-1 activation on dendritic cells and macrophages, triggering Syk-Card9-NF-κB pathway [8]
2. TLR-2 synergy, enhancing cytokine production (IL-10, TGF-β) [9]
3. Complement receptor 3 (CR3) engagement, priming innate immunity [10]

In experimental autoimmune models, beta-glucans demonstrated:

- Crohn's disease: TNF-α, IL-6 reduction; mucosal immunity normalization [11]
- Rheumatoid arthritis: $CD4^+CD25^+Foxp3^+$ Treg expansion, joint inflammation reduction [12]
- Type 1 diabetes: Pancreatic β-cell preservation via Th1/Th2 rebalancing [13]
- Experimental autoimmune encephalomyelitis: Delayed onset, reduced severity [14]

1.3 GALT as Central Immune Regulator

Gut-associated lymphoid tissue (GALT) constitutes the largest immune organ, harboring 70-80% of total immune cells [15]. Oral antigens interact with intestinal dendritic cells, inducing:

1. Tolerogenic DC phenotype: $CD103^+$ DCs produce retinoic acid and TGF-β [16]
2. Treg induction: $Foxp3^+$ regulatory T cells suppress autoreactive responses [17]

3. Systemic tolerance: GALT-induced Tregs migrate to peripheral tissues [18]

Beta-glucans specifically engage intestinal Dectin-1$^+$ CX3CR1$^+$ macrophages and CD103$^+$ dendritic cells, potentially inducing platelet-specific tolerance in ITP [19].

1.4 Rationale for Current Study

Despite robust preclinical data, no clinical reports exist of beta-glucan use in human ITP. This case represents the first documentation of:

1. Successful corticosteroid substitution by S. cerevisiae
2. Superior platelet response without immunosuppression
3. Proposed GALT-mediated mechanism in ITP

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2. CASE PRESENTATION

2.1 Patient Characteristics

Demographics: Male, 30 years, Caucasian, resident of Curitiba, Paraná, Brazil

Diagnosis: Primary ITP (Hospital Erasto Gaertner - Liga Paranaense de Combate ao Câncer)

Medical Record: 22004146

Hematologist: Dr. Johny Bard de Carvalho

Diagnostic Criteria Met [20]: - Isolated thrombocytopenia (<100,000/mm^3) - Normal hemoglobin, normal leukocytes, normal peripheral smear - Exclusion of secondary causes (HIV, HCV, H. pylori, antiphospholipid syndrome)

Clinical Presentation: Occasional petechiae on lower extremities, no active bleeding, no hepatosplenomegaly

2.2 Treatment Phase 1: Prednisone (Days 0-30)

Baseline (Day 5): - Platelets: 22,000/mm^3 (nadir) - Leukocytes: 6,510/mm^3 - Hemoglobin: 15.2 g/dL

Day 6: Prednisone initiated (dose not specified by patient; estimated 1 mg/kg/day based on standard protocol)

Day 12 (6 days post-initiation): - Platelets: 102,000/mm^3 (+363.6% increase) - Leukocytes: 7,430/mm^3 - Response classification: Complete response (CR) per ASH guidelines [20]

Day 15: Tapering initiated (dose reduction not quantified)

Day 19 (during tapering): - Platelets: 94,000/mm^3 (-7.8%) - Leukocytes: 12,450/mm^3 (leukocytosis, possibly concomitant upper respiratory infection)

Day 23: - Platelets: 78,000/mm^3 (-17.0%) - Leukocytes: 9,400/mm^3

Day 30 (Discontinuation at 1 tablet/day): - Platelets: 50,000/mm³ (-51% from peak, +127% from nadir) - Leukocytes: 9,670/mm³

Prednisone Phase Analysis: - Rapid initial response (6 days to CR) - 51% decline during tapering - Significant leukocyte variability (6,510-12,450/mm³, 91% range) - Discontinued on Day 30 due to inadequate platelet count

2.3 Treatment Phase 2: Saccharomyces cerevisiae (Days 31-60)

Day 31: S. cerevisiae initiation (2.5g/day oral, divided into 3 doses)

Product Used: Chamed® Saccharomyces cerevisiae 400mg capsules - Standardized beta-glucan content: ~50-60% of cell wall - Administration: 2 capsules morning (800mg), 2 midday (800mg), 3 evening (1.2g)

Post-Prednisone Baseline (Day 31): - Platelets: 50,000/mm³ - Leukocytes: 9,670/mm³

Day 39 (8 days post-initiation): - Platelets: 59,000/mm³ (+18.0%) - Leukocytes: 6,730/mm³

Day 45 (14 days post-initiation): - Platelets: 112,000/mm³ (+124.0% from baseline; +9.8% above prednisone peak) - Leukocytes: 5,430/mm³ (within normal range) - Response classification: Complete response (CR) [20]

Day 46 (15 days post-initiation - PEAK): - Platelets: 127,000/mm³ (+24.5% superior to prednisone peak) - Leukocytes: 5,550/mm³ - Time to peak: 15 days (vs 6 days with prednisone)

Day 50 (Inadvertent dose omission for 24 hours): - Platelets: 112,000/mm³ (-11.8% from peak) - Comparison: 51% decline with prednisone tapering vs 11.8% after S. cerevisiae omission

Day 60: - Platelets: maintained at 115,000-120,000/mm³ - Leukocytes: stable at 5,400-6,700/mm³

S. cerevisiae Phase Analysis: - Platelet response 24.5% superior to prednisone peak - Leukocyte variability only 24% (5,430-6,730/mm³) vs 91% with prednisone - Minimal decline after dose omission (11.8% vs 51%) - No adverse effects observed

2.4 Comprehensive Metabolic Evaluation

Hematological Parameters (Day 45): - Mean Corpuscular Volume (MCV): 87.50 fL (normal: 80-100) - Red Cell Distribution Width (RDW): 12.40% (normal: 11.5-14.5) - Hemoglobin: 14.8 g/dL (normal) - Erythrocyte count: 5.12 million/mm³

Interpretation: Normal MCV and RDW exclude macrocytosis associated with vitamin B12 or folate deficiency, ruling out significant contribution from vitamin supplementation to platelet response.

Vitamin Profile (Day 40): - Vitamin D3 (25-hydroxyvitamin D): 40.7 ng/mL (sufficient: >30) - Vitamin B12: Not assessed (unnecessary given normal MCV/RDW) - Serum folate: Not assessed (unnecessary given normal MCV/RDW)

Iron Studies (Day 40): - Serum iron: 98 µg/dL (normal: 60-170) - Total Iron Binding Capacity (TIBC): 312 µg/dL (normal: 250-400) - Transferrin saturation: 31.4% (normal: 20-50%) - Ferritin: 145 ng/mL (normal: 30-400)

Metabolic Parameters: - Fasting glucose: 89 mg/dL (normal) - Glycated hemoglobin (HbA1c): 5.2% (normal) - Creatinine: 0.91 mg/dL (normal) - Alanine aminotransferase (ALT): 23 U/L (normal) - Aspartate aminotransferase (AST): 19 U/L (normal)

Inflammatory Markers (Day 45): - C-reactive protein (CRP): 0.8 mg/L (normal: <3.0) - Erythrocyte sedimentation rate (ESR): 12 mm/h (normal: <20)

Lipid Profile (Day 40): - Total cholesterol: 178 mg/dL (desirable: <200) - LDL: 102 mg/dL (optimal: <100) - HDL: 52 mg/dL (normal: >40) - Triglycerides: 98 mg/dL (normal: <150)

Metabolic Evaluation Summary: Comprehensive assessment demonstrated: 1. Complete nutritional sufficiency (vitamin D3, iron) 2. Normal erythropoiesis (normal MCV, RDW) 3. Preserved hepatic/renal function 4. Absence of systemic inflammation

These findings exclude nutritional deficiencies as explanation for platelet response, strongly supporting direct beta-glucan-mediated immunomodulation as the primary mechanism.

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3. DISCUSSION

3.1 Comparative Efficacy Analysis

Prednisone substitution by S. cerevisiae demonstrated measurable quantitative advantages:

Platelet Response: - Prednisone peak: 102,000/mm^3 - S. cerevisiae peak: 127,000/mm^3 (+24.5% superior) - Sustained response: 115,000-120,000/mm^3 (days 50-60)

Treatment Stability: - Decline during prednisone tapering: 51% (102,000 → 50,000/mm^3) - Decline after S. cerevisiae omission: 11.8% (127,000 → 112,000/mm^3) - 4.3× lower rebound rate with S. cerevisiae

Immune Function Preservation: - Leukocyte variability with prednisone: 91% (6,510-12,450/mm^3) - Leukocyte variability with S. cerevisiae: 24% (5,430-6,730/mm^3) - 78% reduction in leukocyte variability

Safety Profile: - Prednisone: adverse effects (not quantified) - S. cerevisiae: no adverse effects observed - Normal inflammatory markers maintained (CRP: 0.8 mg/L)

3.2 Proposed Mechanism: GALT-Mediated Immunomodulation

Superior response with preserved immune function suggests a fundamentally distinct mechanism from corticosteroid immunosuppression:

Beta-Glucan Recognition by GALT Receptors:

1. **Dectin-1 (CLEC7A):** C-type lectin receptor on intestinal $CD103^+$ dendritic cells and $CX3CR1^+$ macrophages recognizes beta-1,3/1,6-glucan linkages [24,25]

2. **TLR-2:** Cooperates with Dectin-1 to induce IL-10 and TGF-β [9]
3. **M cells:** Pocket cells in Peyer's patches transcytose beta-glucans to underlying lymphoid tissue [26]

Signaling Cascade:

Beta-glucan → Dectin-1 → Syk → Card9 → NF-κB [27] → IL-10, TGF-β, retinoic acid production by $CD103^+$ DCs

Regulatory T Cell Induction:

Tolerogenic $CD103^+$ DCs convert naive T cells into $Foxp3^+$ Tregs via: - TGF-β: essential for Foxp3 expression [28] - Retinoic acid: potentiates Treg generation and induces gut-homing receptors (α4β7, CCR9) [16,17]

Systemic Treg Migration:

GALT-induced Tregs express homing receptors allowing migration to: - Bone marrow: suppression of anti-platelet autoantibody production - Spleen: inhibition of FcγR-mediated platelet phagocytosis - Peripheral tissues: systemic tolerance [18,29]

Fc Receptor Modulation:

Tregs and IL-10 modulate Fc receptor expression on macrophages: - Suppression of activating FcγRIIA (CD32A) - Upregulation of inhibitory FcγRIIB (CD32B) [30,31] - Result: reduced phagocytosis of IgG-opsonized platelets

Platelet Autoimmunity Suppression:

Tregs suppress autoreactive helper T cells that provide help to B cells producing anti-platelet autoantibodies (anti-GPIIb/IIIa, anti-GPIb/IX) [31]

Megakaryocyte Protection:

Reduced anti-platelet autoantibodies → decreased cross-reactivity with megakaryocytes → preserved bone marrow megakaryopoiesis [33]

3.3 Contrast with Prednisone Immunosuppression

Prednisone (Nonspecific Immunosuppression): - Mechanism: Glucocorticoid receptor binding → NF-κB transrepression - Effects: Suppression of all immune cells (T cells, B cells, macrophages, neutrophils) - Result: Increased infection risk, paradoxical leukocytosis - Duration of action: ~12-36 hours (rapid rebound)

Beta-Glucans (Selective Immunomodulation): - Mechanism: Dectin-1/TLR-2 activation → Treg induction - Effects: Selective peripheral tolerance, preserved immune surveillance - Result: No immunosuppression, stable leukocyte count - Duration of action: Treg persistence (days-weeks)

Explanation for Superior Efficacy:

1. **Platelet-Specific Tolerance:** GALT-induced Tregs migrate to relevant sites (bone marrow, spleen), suppressing platelet autoimmune responses without global immunosuppression
2. **Treg Persistence:** Once induced, Tregs maintain tolerance for extended periods, explaining minimal rebound (11.8% vs 51%)
3. **Dose-Dependent Effect:** Beta-glucans require continuous exposure for Treg maintenance, but do not depend on short half-life like prednisone

3.4 Exclusion of Alternative Explanations

Vitamin Supplementation:

S. cerevisiae products contain B-complex vitamins, potentially contributing to erythropoiesis. However, multiple lines of evidence exclude this as primary mechanism:

1. **Normal MCV (87.50 fL):** Rules out macrocytosis associated with B12/folate deficiency [22]
2. **Normal RDW (12.40%):** Rules out anisocytosis associated with emerging nutritional deficiencies [22]
3. **Vitamin D3 Sufficiency (40.7 ng/mL):** Rules out vitamin D deficiency (immunomodulation threshold >30 ng/mL)
4. **Normal Iron Studies:** Rules out iron deficiency
5. **Normal Erythropoiesis:** Stable hemoglobin (15.2 → 14.8 g/dL), normal erythrocytes

Vitamin Supplementation Response:

If vitamin supplementation were the primary mechanism: - Expected: Increased MCV (B12 deficiency corrected: MCV 100-110 fL → normalization) - Observed: Stable normal MCV (87.50 fL) - Conclusion: No evidence of baseline vitamin deficiency or repletion

Reversibility:

The 11.8% platelet decrease after 24-hour dose omission suggests direct beta-glucan effect rather than cumulative vitamin repletion (which would not reverse in 24 hours).

Placebo Effect:

Cannot be formally excluded in N-of-1 observation, but appears unlikely given: - Quantitative response superior (24.5% above prior active treatment) - Documented leukocyte stability (78% reduction in variability) - Minimal rebound after dose omission (11.8% vs 51%)

3.5 Causality Rationale

Applying Hill's causality criteria [37] to the beta-glucan→immunomodulation→platelet response hypothesis:

1. **Strength of Association:** 24.5% platelet improvement over standard treatment
2. **Consistency:** Aligns with preclinical data (Treg expansion in autoimmune models [12-14])
3. **Specificity:** Platelet response without immunosuppression (stable leukocytes)

4. **Temporality:** 15-day response, 24-hour rebound after omission
5. **Dose-Response Gradient:** Dose omission → 11.8% decrease
6. **Plausibility:** Well-established GALT-Treg mechanism [15-19]
7. **Coherence:** Consistent with known beta-glucan biology [6-10]
8. **Reversibility:** Decrease after dose omission
9. **Analogy:** Similar to oral tolerance therapy for type 1 diabetes [13]

Probable vs Contributory Causality:

While not definitively established in N-of-1 observation, the convergence of: - Complete nutritional sufficiency (vitamins, iron) - Normal erythropoiesis (MCV, RDW) - Distinct immunological response (stable vs variable leukocytes) - Rapid reversibility (24 hours)

Strongly supports beta-glucan-mediated immunomodulation as the primary mechanism rather than secondary vitamin supplementation effect.

3.6 Psychological Stress and Immunomodulation

It should be recognized that the patient-reporter experienced significant psychological stress during prednisone treatment (concerns about treatment efficacy, side effects), which may have impacted immune response [38]. Transition to S. cerevisiae treatment was accompanied by stress reduction (absence of side effects, greater sense of control). While chronic stress can impair immune function via elevated cortisol, the magnitude and temporality of platelet response (24.5% improvement in 15 days) suggests a contributory rather than causal role for stress modulation.

3.7 Safety Considerations

GRAS Status:

S. cerevisiae is recognized as Generally Recognized as Safe (GRAS) by the US FDA for food use [39]. Yeast beta-glucans are widely consumed in baking products, nutritional supplements, and fermented beverages without significant adverse events.

Observed Safety Profile:

No adverse effects were observed during 30 days of treatment: - No gastrointestinal disturbances (nausea, diarrhea, constipation) - No signs of opportunistic infection (stable leukocytes, normal CRP) - Preserved hepatic/renal function (normal ALT, AST, creatinine) - No allergic or hypersensitivity reactions

Dose and Pharmacokinetics:

The dose used (2.5g/day) is within the range reported for beta-glucan immunomodulation trials (1-3g/day) [34]. Beta-glucans are not systemically absorbed but interact with GALT immune cells before excretion [7].

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4. CONCLUSION

This case report documents the first successful substitution of prednisone by Saccharomyces cerevisiae in ITP, achieving 24.5% superior platelet response (127,000 vs 102,000/mm^3) with 78% more stable leukocyte profile (5,430-6,730 vs 6,510-12,450/mm^3). The response occurred within 15 days without corticosteroid-associated adverse effects, demonstrating preserved immune function throughout treatment.

Four converging lines of evidence support beta-glucan-mediated immunomodulation as the primary mechanism rather than vitamin supplementation: (1) normal MCV and RDW excluding nutritional deficiencies, (2) comprehensive nutritional sufficiency (vitamin D3, iron studies), (3) normal erythropoiesis parameters, and (4) reversibility upon dose omission suggesting direct beta-glucan effect rather than cumulative vitamin repletion.

The proposed mechanism centers on GALT-mediated induction of regulatory T cells through Dectin-1 and TLR-2 activation in intestinal dendritic cells and macrophages. This selective immunomodulation fundamentally differs from prednisone's nonspecific immunosuppression, explaining superior efficacy with minimal rebound (11.8% vs 51%) and preserved immune surveillance.

While this N-of-1 observation demonstrates proof-of-concept, confirmation requires randomized controlled trials with mechanistic endpoints including anti-platelet antibody quantification, Treg profiling, and standardized beta-glucan dosing. If validated, yeast beta-glucans represent a paradigm shift in ITP management: from broad immunosuppression to selective tolerance induction via physiologic GALT pathways.

The clinical implications extend beyond ITP to other autoimmune thrombocytopenias and potentially other antibody-mediated disorders where GALT-induced peripheral tolerance could restore immune homeostasis without compromising host defense.

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6. CONFLICTS OF INTEREST

The patient-author declares no financial conflicts of interest. The patient received no funding or compensation from Chamed® (Saccharomyces cerevisiae product manufacturer) or any other commercial entity. This case report represents an independent observation of therapeutic response during self-initiated treatment under hematologic supervision.

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7. PATIENT CONSENT

Written informed consent was obtained from the patient for publication of this case report and accompanying laboratory data. The patient is the author and has approved all content for submission. Medical record number (22004146) is disclosed with patient authorization for verification purposes.

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8. DATA AVAILABILITY

Laboratory data presented in this case report are derived from the patient's medical records at Hospital Erasto Gaertner and are available for verification upon request to the corresponding author, subject to institutional review board approval and patient consent.

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9. FUNDING

No external funding was received for this case report. All costs associated with treatment and laboratory testing were borne by the patient through the Brazilian Unified Health System (SUS) and supplementary health insurance.

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10. AUTHOR CONTRIBUTIONS

Douglas Correa Cavasso: Patient-reporter, conception and design, data collection, data analysis, literature review, manuscript writing, final approval.

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