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Inebilizumab for Treatment of IgG4-Related Disease

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inebilizumab for Treatment of IgG4-Related Disease

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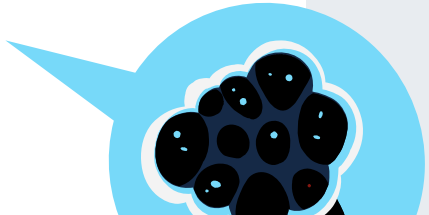


STUDY OBJECTIVES

•The study aimed to evaluate the therapeutic potential of inebilizumab, a humanized monoclonal antibody targeting CD19+ B cells, for patients with IgG4-related disease, an immune-mediated fibroinflammatory disorder with limited treatment options. The specific objectives were as follows:

•**Primary Objective**:
To determine the efficacy of inebilizumab in reducing the incidence of treated, adjudicated disease flares over a 52-week period in patients with active IgG4-related disease,
•**Secondary Objectives**:

•Evaluating the annualized flare rate of IgG4-related disease.
•Assessing treatment-free and glucocorticoid-free complete remission at the end of the treatment period.
•Determining the safety profile and adverse events associated with inebilizumab.

AIM OF THE STUDY

- To investigate the efficacy and safety of inebilizumab, a CD19-targeted monoclonal antibody, in **reducing disease flares** and **achieving sustained remission** in patients with IgG4-related disease, while **minimizing the need for glucocorticoids** and other immunosuppressive therapies.

- SAMPLE SIZE :
- A total of 135 participants with IgG4-related disease underwent randomization:68 participants were assigned to receive inebilizumab and 67 were assigned to receive placebo.

- The study was conducted across **80 clinical sites in 22 countries**, which increases the generalizability of the results.

- The trial spanned a **52-week treatment period**, providing a comprehensive assessment of both short-term efficacy and longer-term disease control.

STUDY DESCRIPTION

- Phase 3, multicenter, double-blind, randomized, placebo-controlled clinical trial.

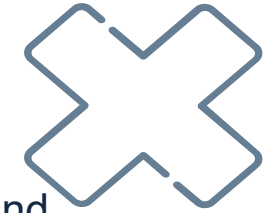
- Participants were randomized in a 1:1 ratio to receive either inebilizumab or placebo. Inebilizumab was administered as a 300-mg intravenous infusion on days 1 and 15, followed by an additional dose at week 26 during the 52-week treatment period

- Participants were enrolled based on the 2019 (ACR-EULAR) classification criteria for IgG4-related disease.

INCLUSION CRITERIA

- Informed Consent: Willingness to provide written informed consent to participate in the study.
- Age: Adults aged 18 years or older.
- Diagnosis: Confirmed diagnosis of IgG4-related disease based on the 2019 ACR-EULAR classification criteria.
- Disease Activity: Evidence of active disease with involvement of at least two organ systems.
- Glucocorticoid Treatment: Requirement for glucocorticoid treatment due to active disease at screening or randomization.
- Disease Flare: Participants must be experiencing a flare of IgG4-related disease that warrants initiation or continuation of glucocorticoids.

EXCLUSION CRITERIA



•**Use of Background Immunosuppressants**: Participants who were on background immunosuppressive therapy other than glucocorticoids were excluded. This was to ensure that the effects of inebilizumab could be assessed without interference from other medications.

•**Severe Organ Dysfunction**: Patients with significant dysfunction of critical organs were excluded to minimize risk and ensure the safety of participants during the study.

•**Active Infections**: Individuals with active or uncontrolled infections (e.g., bacterial, viral, or fungal) were not allowed to participate. This was crucial as inebilizumab targets B cells and could increase susceptibility to infections.

•**Malignancies**: A history of active malignancy or those with unresolved cancers within the past 5 years (except for non-melanoma skin cancer) were excluded due to potential interference with immune function.

EXCLUSION CRITERIA

- **Hypersensitivity to Inebilizumab or Related Compounds**: Participants with a known hypersensitivity or allergic reaction to inebilizumab, any of its components, or related monoclonal antibody therapies were excluded.
- **Pregnancy or Lactation**: Pregnant or breastfeeding women were excluded to avoid potential harm to the fetus or infant.
- **Severe Allergic Reactions to Infusions**: Participants who had a history of severe reactions to infusions, such as anaphylaxis, were excluded to prevent serious adverse events during the study.
- **Neurological Conditions**: Patients with severe neurological disorders that could complicate treatment or affect outcomes were excluded.

EXCLUSION CRITERIA

- **Previous Use of Rituximab or Other B-cell Depletion Therapies**: Individuals who had previously received rituximab or other CD20-targeted therapies for IgG4-related disease were excluded due to potential overlap in treatment mechanisms.

- **Other Autoimmune or Systemic Diseases**: Patients with other significant autoimmune diseases or systemic conditions that might interfere with the study or treatment evaluation were excluded.

PRIMARY END POINTS

Primary End Point	Definition	Key Results
Time to First Treated and Adjudicated Disease Flare	Time from randomization to the first flare requiring treatment, as adjudicated by an expert panel.	Hazard ratio (HR): **0.13** (95% CI: 0.06–0.28, **P < 0.001**) indicating an **87% risk reduction**.
Flare Definition	New or worsening clinical features confirmed by symptoms, physical exam, imaging, lab, or pathology evidence.	Only **10% of patients** in the inebilizumab group experienced flares vs. **60% in placebo group**.
Treatment Required for Flare	Any therapy initiated for managing active disease symptoms associated with IgG4-related disease.	Median time to flare was significantly delayed in the inebilizumab group

Secondary End Points

	Key Results
Annualized Flare Rate	Reduced by **86%** in inebilizumab group (Rate Ratio: **0.14**, 95% CI: 0.06–0.31, **P < 0.001**).
Flare-Free, Treatment-Free Complete Remission	Achieved by **57%** in inebilizumab group vs. **22%** in placebo group (Odds Ratio: **4.68**, **P < 0.001**).
Flare-Free, Glucocorticoid-Free Complete Remission	Achieved by **59%** in inebilizumab group vs. **22%** in placebo group (Odds Ratio: **4.96**, **P < 0.001**).
Cumulative Glucocorticoid Dose	Total dose: **118.3 mg** in inebilizumab group vs. **1384.5 mg** in placebo group.
Serious Adverse Events	Reported in **18%** of inebilizumab group vs. **9%** in placebo group.

Primary and Key Secondary Efficacy End Points

Table 2. Primary and Key Secondary Efficacy End Points (Full Analysis Population).

End Point	Inebilizumab (N=68)	Placebo (N=67)	Effect vs. Placebo (95% CI)	P Value
Primary: time to first treated and adjudicated IgG4-related disease flare — no. (%)	7 (10.3)	40 (59.7)	0.13 (0.06–0.28)*	<0.001
Key secondary				
Annualized flare rate: treated and adjudicated IgG4-related disease flares — no. (95% CI)	0.10 (0.05–0.21)	0.71 (0.53–0.94)	0.14 (0.06–0.31)†	<0.001
Flare-free, treatment-free complete remission at wk 52 — no. (%)‡	39 (57.4)	15 (22.4)	4.68 (2.21–9.91)§	<0.001
Flare-free, glucocorticoid-free complete remission at wk 52 — no. (%)¶	40 (58.8)	15 (22.4)	4.96 (2.34–10.52)§	<0.001

RESULTS OF THE STUDY

- **Only 10% of participants** in the inebilizumab group experienced a disease flare during the 52-week study period, compared to 60% in the placebo group.

- Inebilizumab significantly delayed the time to the first disease flare, with the median not reached in the inebilizumab group due to the low flare incidence.

Table: CD20+ B-Cell and IgG4 Levels Over Time During the Treatment Period

Time Point (Weeks)	CD20+ B-Cell Levels (% of Baseline)	Serum IgG4 Levels (% Change from Baseline)
Baseline	100%	100%
Week 2	10%	−40%
Week 4	5%	−55%
Week 8	3%	−70%
Week 20	1%	−80%
Week 26	1%	−85%
Week 38	1%	−85%
Week 46	2%	−82%
Week 52	5%	−80%

CD20+ B-Cell and IgG4 Levels Over Time During the Treatment Period

- The rapid and sustained depletion observed demonstrates the pharmacodynamic effect of inebilizumab.
- Serum IgG4 Levels: The reduction in serum IgG4 levels reflects the therapeutic impact of inebilizumab in controlling IgG4-related disease activity.
- **Key Observations:**
- **CD20+ B-cell levels were reduced to <5% of baseline** within 4 weeks and remained suppressed through week 52.
- Serum IgG4 levels showed a significant and sustained decline, indicating effective disease control.

Trend results

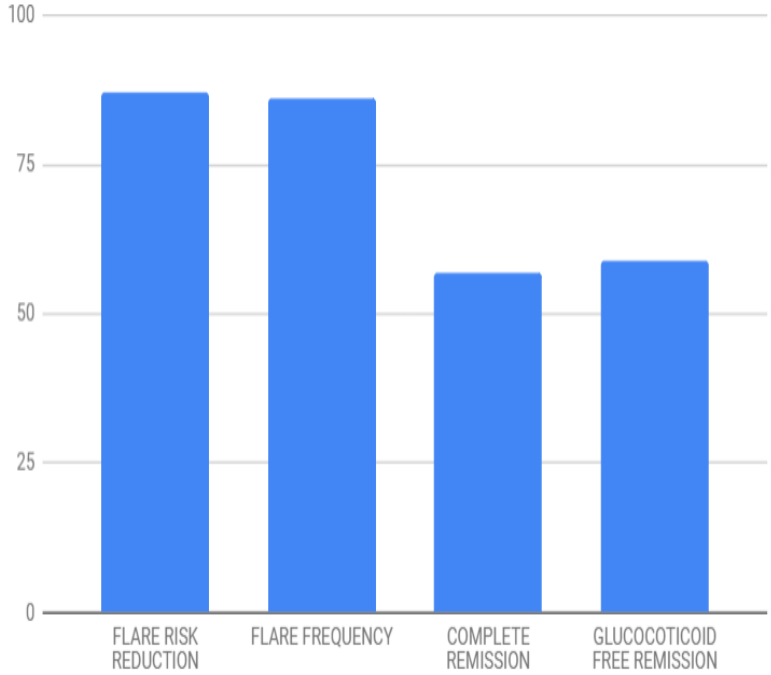
The incidence of flares was markedly lower in the inebilizumab group (**10%**) than in the placebo group (**60%**).

87% reduction in flare risk.

86% reduction in flare frequency.

57% of inebilizumab-treated participants achieved treatment-free remission

59% of participants in the inebilizumab group achieved Glucocorticoid free complete remission



ADVERSE EFFECTS

- AEs were reported in 18% of inebilizumab-treated participants compared to 9% in the placebo group.
- Common SAEs included infections (e.g., urinary tract infections and COVID-19) and infusion-related reactions.
- **Lymphopenia**

- Reported in **16%** of the inebilizumab group and **9%** of the placebo group.
- Most cases were asymptomatic and reversible without requiring intervention.

ADVERSE EFFECTS

Adverse Event	Inebilizumab Group (N = 68)	Placebo Group (N = 67)
Common Adverse Events		
COVID-19	16 (24%)	13 (19%)
Lymphopenia	11 (16%)	6 (9%)
Urinary Tract Infection	8 (12%)	4 (6%)
Headache	6 (9%)	7 (10%)
Abdominal Pain	4 (6%)	7 (10%)
Arthralgia	4 (6%)	7 (10%)
Upper Respiratory Tract Infection	4 (6%)	8 (12%)
Diarrhea	3 (4%)	9 (13%)
Asthenia	2 (3%)	8 (12%)

Table: Adverse Events of Special Interest During the Treatment Period

Adverse Event	Inebilizumab Group (N = 68)	Placebo Group (N = 67)
Cytopenias		
Lymphopenia	13 (19%)	6 (9%)
Neutropenia	4 (6%)	2 (3%)
Anemia	2 (3%)	2 (3%)
Thrombocytopenia	1 (1%)	2 (3%)

LIMITATIONS OF THE STUDY

- **Short Duration of the Study**
  - The study was conducted over **52 weeks**, which, although sufficient for assessing short-term efficacy and safety, may not capture the long-term effects of inebilizumab, particularly in terms of disease relapse or late-onset adverse events.

- **Single Trial Design**
  - The study relied on a **single phase 3 trial** with **135 participants**. While the results are statistically significant, the sample size may limit the ability to detect rare adverse events or variations in treatment response across different populations.

- **No Comparison to Other Active Treatments**
  - The study compared inebilizumab to **placebo** but did not include an active comparator such as **rituximab**, which has been used off-label in IgG4-related disease.

LIMITATIONS OF THE STUDY

- **Exclusion of Certain Patient Populations**
- Patients with **severe organ dysfunction**, **active infections**, or **malignancies** were excluded, limiting the generalizability of the results to those with more severe or complex comorbidities.

- **Safety Profile in Larger Populations**

- The **long-term incidence of serious adverse events** (such as infections or malignancies) may not be fully understood with the sample size and study duration.

- Furthermore, the impact of inebilizumab on **immunocompromised** patients and those with coexisting conditions may differ in real-world settings.

- Longer-term data are needed to establish the safety profile of inebilizumab in the treatment of IgG4-related disease and to characterize the patterns of B-cell and immunoglobulin changes; **for these reasons, a 3-year open-label period is ongoing.**

CONCLUSION

- Despite these limitations, the study provides robust evidence of inebilizumab's efficacy and safety for treating **IgG4-related disease**, establishing it as a promising therapeutic option.

- However, further research addressing the above limitations, particularly through long-term trials, active comparative studies, and broader patient inclusion, would help refine the understanding of inebilizumab’s role in managing this complex disease.

THANK YOU