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Targeted immunomodulatory and biologic therapies for treatment-resistant granuloma annulare: a systematic review

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Introduction
Granuloma annulare (GA) is a chronic, inflammatory granulomatous skin disease. The incidence of GA is estimated at 0.04%, with a predilection for women during their fifth decade of life. In many cases, particularly in generalized forms, GA is resistant to currently used standard therapies, which are largely based on case reports and clinical experience, and no evidence-based guideline exists for the management of generalized GA. Increasing insight into GA pathogenesis, including the role of Th1- and Th2-mediated cytokine signaling via the JAK-STAT pathway, supports the rationale for targeted immunomodulatory and biologic therapies. The aim of this systematic review was to summarize and critically assess the available literature and evidence on innovative immunomodulatory and biologic treatment options for GA.

Materials and Methods
This systematic review was conducted according to PRISMA guidelines and registered in PROSPERO. A search of PubMed, Embase and Cochrane databases was performed for studies published between January 2020 and December 2025, using relevant MeSH terms and keywords related to GA and targeted or biologic therapies. Original studies, case reports, and case series involving adults treated with immunomodulatory or biologic agents were included. Eligibility assessment and data extraction were performed independently by two reviewers.

Results
Seventeen publications were included, comprising 42 patients with GA treated with biologic or targeted therapies. The majority were female (71%), aged 26-79 years, with generalized disease refractory to prior treatment in most cases. Janus kinase (JAK) inhibitors were the most frequently administered therapy, used in 36/42 patients (87%). The analysis included tofacitinib, upadacitinib, abrocitinib, baricitinib, and deucravacitinib. Most patients treated with JAK inhibitors achieved significant clinical improvement, typically within 2-6 weeks, with complete or near-complete clearance reported in the majority of cases. Biologic agents were used less frequently. Tumor necrosis factor-alpha inhibitors were administered in three patients and were also associated with clinical improvement, although relapses were reported. Dupilumab, apremilast, and tildrakizumab were each reported in single patients, with variable efficacy. Adverse events were uncommon and mild. Laboratory abnormalities, mainly hyperlipidemia, were reported in three patients, with pharmacologic management required in one case. No serious adverse events leading to treatment discontinuation were observed.

Conclusions
Targeted biologic and immunomodulatory therapies, particularly JAK inhibitors, appear to be effective and well-tolerated options for patients with GA resistant to conventional treatment. Most reported patients achieved relevant clinical improvement, with complete or near-complete clearance. However, current evidence is limited to case reports and

small case series, emphasizing the need for further research, especially prospective controlled studies