ILD Collaborative

Project ECHO

Sarcoidosis: Beyond First Line Therapy

ECHO Didactic Series

April 16, 2025

Fiona Gibbons, MD

Disclosures

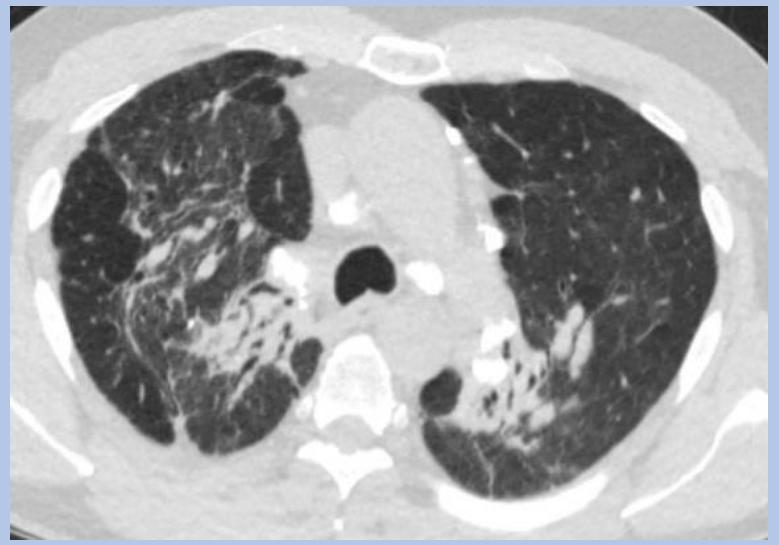
- PI for **Efficacy and Safety of Intravenous Efzofitimod in Patients With Pulmonary Sarcoidosis**
- Sponsor: aTyr Pharma, Inc.
- Research Funds

Therapeutic Goals

- Who needs treatment?
- We cannot cure the disease, only put it at bay
- Main goal of treatment should be to improve quality of life or symptoms
- Prevent harm

Treatment Indications: Pulmonary Sarcoid

- Worsening symptoms
- Deterioration in pulmonary function on serial testing
  - decline in TLC $\geq$ 10%
  - FVC $\geq$ 15%
  - DLCO $\geq$ 20%, worsening gas exchange
- Progression in radiograph, evidence of fibrosis
- Signs of pulmonary hypertension



Treatment Indications: Extrapulmonary Sarcoid

- Cardiac disease
- Neurologic disease
- Ocular disease refractory to topical therapy
- Disfiguring skin disease
- Hypercalcemia
- Renal sarcoid
- Severe constitutional symptoms

Treatment Since 1960s

- No agent has been approved specifically for treatment of sarcoidosis
- Prednisone 0.5-1.0 mg/kg IBW (20-40 mg) for 1-3 months, reassess, taper over several months goal 6-12 months of treatment

European Respiratory Journal 2023 62: 2300198

Summary Original Study Steroids

Main conclusions:

- Steroid treatment may relieve dyspnea, but only in the minority
- Prolonged treatment with corticosteroids appears to modify the course of progressive pulmonary sarcoidosis
- Steroid treatment does not increase the chance of complete remission

SARCORT: High-dose (40 mg) *v* low-dose (20 mg) prednisolone for treating sarcoidosis

- RCT 40 mg v. 20 mg prednisolone over 6mo
- Primary outcome: frequency of relapse/treatment failure @ 18 mo
- Secondary: Overall response, change in FVC, HRQoL score
- No difference in frequency or mean time to outcome, FVC, adverse effects, or HRQoL scores

European Respiratory Journal 2023 62: 2300198

Outcome of treatment

- RCT have not shown substantial long-term benefit in PFT or reduced disability
- Relapse rate is high
- Among those who are treated, >50% will need treatment in the future

Steroid Sparing Agents/Alternative Agents

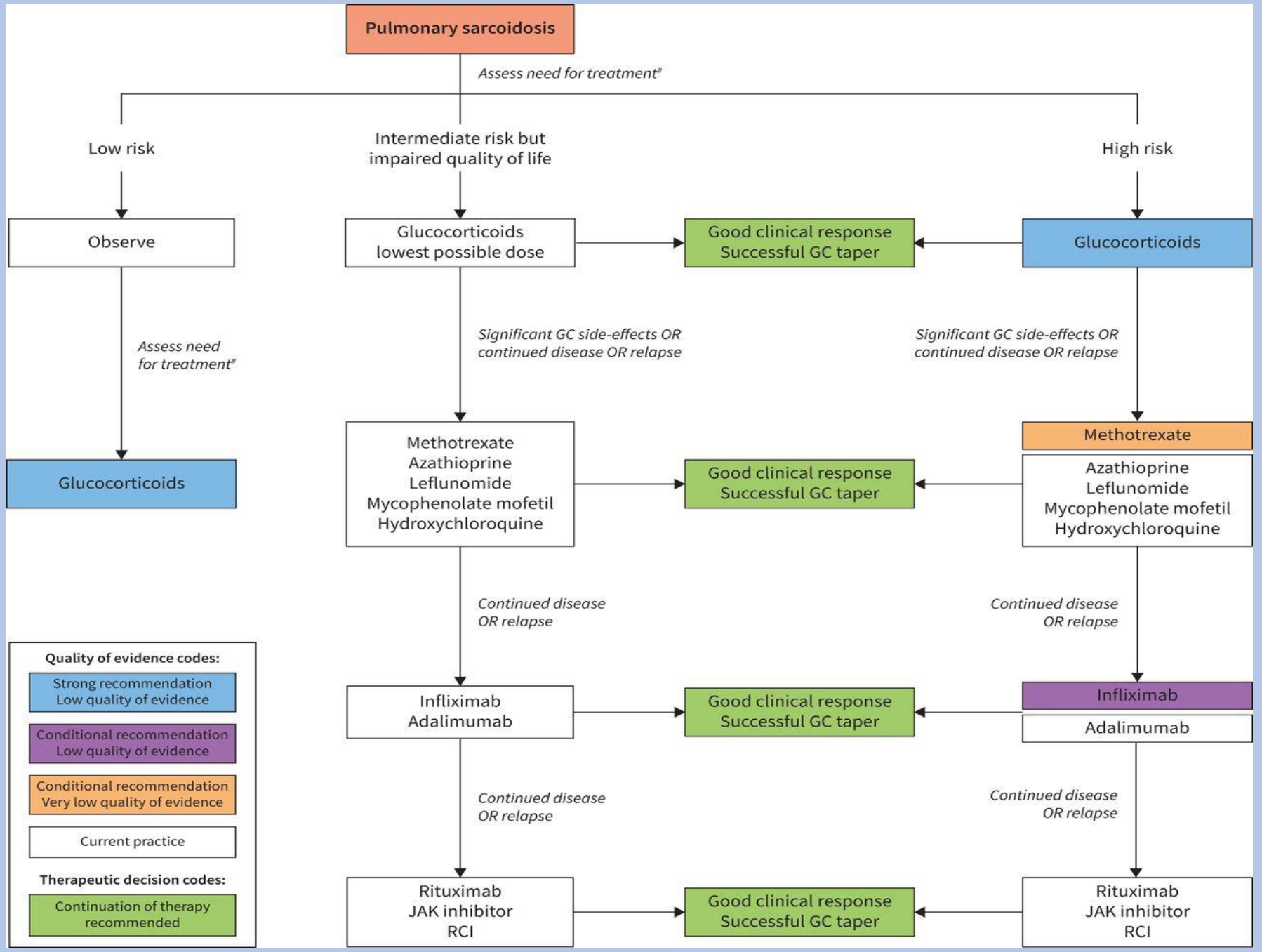
- **Methotrexate (refractory sarcoid, ocular)**
- **Azathioprine (refractory disease)**
- Hydroxychloroquine (skin disease, hypercalcemia)
- Cyclophosphamide (refractory dz, neurologic dz)
- Mycophenolate
- NSAIDS (E. nodosum)
- Ketoconazole (hypercalcemia)
- Minocycline (skin disease)
- Thalidomide (STEPS)
- Leflunomide (prevents de novo synthesis of pyrimidines and inhibits T cell proliferation)

Infliximab

- Human murine chimeric Ab to TNF-α (TNF-α antagonist)
- TNF-α plays a critical role in granulomatous inflammation
- TNF-α is elevated in patients with sarcoid

Infliximab Therapy in Patients with Chronic Sarcoidosis and Pulmonary Involvement

- 138 patients randomized to 3 or 5 mg/kg Infliximab or placebo given on weeks 0, 2, 6, 12, 18, and 24, followed through 52 wks
- Primary endpoint was change from baseline to 24 wks in % predicted FVC
- Infliximab - FVC increased by 2.5% v. no increase in placebo (p=0.038)
- Largest increase in FVC in those with more symptoms, worse baseline FVC, and longer disease duration
- More beneficial in patients receiving immunosuppressants or higher doses of corticosteroids or in those with multiorgan extrapulmonary involvement



Robert P. Baughman et al. Eur Respir J 2021;58:2004079

Rituximab for Sarcoidosis

- Although sarcoidosis is a T-cell-mediated disease, humoral mechanisms may play a role
- Sarcoidosis is often associated with hypergammaglobulinaemia, autoantibody production and circulating immune complexes so B cell depletion may be helpful
- Small prospective, open-label, phase I/II trial of Rituximab in 10 patients had inconsistent responses in terms of FVC and 6MWT

JAK inhibitors

- Macrophage activation leads to granulomatous inflammation
- Overproduction of inflammatory cytokines leads to activation of the JAK-STAT pathway
- Potential benefit at the case report level
- Tofacitinib Hypothesis-generating, Pilot Study for Corticosteroid-Dependent Sarcoidosis
- Open-label Trial of Tofacitinib in Cutaneous Sarcoidosis and Granuloma Annulare

Tofacitinib

- Open-label, proof-of-concept study of tofacitinib as a steroid-sparing therapy in corticosteroid-dependent pulmonary sarcoidosis
- Five patients with corticosteroid-dependent pulmonary sarcoidosis were treated with tofacitinib 5 mg twice daily
- The primary endpoint was a ≥ 50% reduction in corticosteroids at week 16 with no worsening in pulmonary function or respiratory symptoms.
- 60% of patients (3/5) met the primary endpoint
- The three patients who met the primary endpoint each tapered to ≤ 5 mg/day prednisone, respiratory symptoms improved, and spirometry remained stable

Repository Corticotropin (ACTHAR GEL)

- Purified preparation of ACTH
- FDA approved in 1952, in 1954 for sarcoid
- Stimulates the adrenal cortex to release glucocorticoids
- Directly stimulates melanocortin receptors on T lymphocytes and macrophages
- May have suppressive effects beyond cortisol stimulation

Repository Corticotropin

- Steroid sparing in two retrospective studies and one prospective study
- Expensive
- Exact mechanism of action unclear
- Side effects include fluid retention, weight gain, muscle weakness, osteoporosis, ulcers, impaired wound healing, hypertension, growth suppression, cushingoid state

Efzofitimod

- A fusion protein comprised of the immunomodulatory domain of **histidyl-tRNA synthetase** fused to the Fc region of a human antibody
- A selective modulator of **neuropilin-2 (NRP2)** that downregulates innate and adaptive immune response in inflammatory disease states
- NRP2 is expressed in neutrophils, dendritic cells, macrophages, including alveolar macrophages, T cells, and B cells

Efzofitimod

- Neuropilin-2 (NRP2) is a cell surface receptor that plays a key role in **lymphatic development** and in regulating inflammatory responses
- NRP2 can bind to multiple ligands and co-receptors to influence various cellular functions such as:
  - type 3 semaphorins and plexins to impact **inflammation and neural development**
  - forms of vascular endothelial growth factor (VEGF) and their receptors, especially VEGF-C and VEGFR3, which are centrally involved in **lymphangiogenesis**

Efzofitimod

- NRP2 expression is upregulated on target immune cells during inflammation (sarcoid granulomas)
- Prevented inflammation and fibrosis in multiple animal models of ILD
- Mediates T cell responses and prevents granuloma formation *in vitro*
- It may play important roles in migration, phagocytosis and efferocytosis, and cell-to-cell interactions

Phase 1b/2a study

- Multiple-ascending dose, double-blind, placebo-controlled study in 37 patients with pulmonary sarcoidosis
- Designed to evaluate the safety, tolerability, immunogenicity and pharmacokinetic profile of multiple doses of ATYR1923 compared to placebo

Efzofitimod

- Outcome data showed the highest dose (5 mg/kg) led to significant improvements in **lung function**, as well as **reduced shortness of breath, cough, and fatigue**, compared to a placebo
- At all three doses tested, efzofitimod was well tolerated and safe
- Efzofitimod lowered the use of corticosteroids by 58%
- 33% of patients at the highest efzofitimod arm were able to taper off steroids completely

EFZO-FIT-Phase 3

- One-year **EFZO-FIT** multi-center, international study enrolled 264 patients with pulmonary sarcoidosis
- Participants were randomly to receive either 3.0 mg/kg or 5.0 mg/kg doses of efzofitimod, or placebo, administered IV monthly for a total of 12 doses
- Primary outcomes will be the effect on **corticosteroid use**
- Secondary objectives include changes in lung function (**FVC**) and other sarcoid symptoms
- FDA – Orphan Drug Status
- August 2022 – Fast Track Designation Status