CAR T-cells to treat autoimmunity
CD19 CAR T-CELLS FOR SLE
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Overview

• Autoimmune diseases background

• Treatment options
  • B cell depletion – why it works and why it doesn’t
  • Is it possible to “cure” autoimmune disease?
  • Developing curative cellular therapies for patients with autoimmune disease

• CD19 CAR T for Autoimmune disease
  • Emerging data in SLE
  • Unique considerations
Autoimmune Disease – Global Impact

• An estimated 4.5% of the world’s population lives with autoimmune disease\(^1\)

• Estimated economic burden of >$100 billion\(^2\)

• Incidence is increasing\(^3,4\)
  • Environmental factors
  • Improved surveillance and diagnoses

• Represents a global unmet medical need for which new therapies are needed

Current Treatment Modalities for Autoimmune Disease

Therapies listed in **bold** represent standard of care therapies commonly used to treat SLE

- **Systemic therapies**
  - Metabolic inhibitors: **mycophenolate mofetil** and methotrexate
  - Immune suppressants: **hydroxychloroquine**, and corticosteroids (**prednisone**), **voclosporin**
  - Cytotoxic therapies: cyclophosphamide

- **Targeted therapies**
  - B cell depletion: rituximab
  - Cytokine blockers: **belimumab** (anti-BAFF) and **anifrolumab** (anti-IFNAR1)
  - T and B cell signaling blockade: BTK and JAK inhibitors

- **These therapies remain largely non-curative, requiring chronic therapy**

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B cell depletion is effective in diseases caused by both T and B cells

WHY?....

....because B cells play a central role in driving (autoreactive) T cell responses

1. Rubin, Bloom and Robinson (2019) B Cell Checkpoints in Autoimmune Rheumatic Diseases; Nat Rev Rheum
Rituximab is not Commonly Curative

WHY?

...because Rituximab does not deplete all B cells within tissues¹

- Difficulty in tissue penetration
- Requirement for effector mechanisms to deploy cytotoxic effect
- Therefore, requires repeat administration
- This induces prolonged B cell aplasia

- Newer generations of anti-B cell depleting agents are emerging – may work better²

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1. Table excerpted from: Crickx et al (2020) Anti-CD20-mediated B-cell Depletion in autoimmune diseases
Rituximab has limited tissue penetrance

RA patients treated with rituximab have incomplete tissue B cell depletion

1. Onno Teng, YK et al. (2007), Immunohistochemical Analysis as a Means to Predict Responsiveness to Rituximab Treatment Arthritis & Rheumatism.
Systemic Lympho-ablation is Potentially Curative,

- A series of randomized controlled studies have been conducted to test lympho-ablation followed by stem cell rescue for refractory autoimmune disease\textsuperscript{1,2}
  - Over 3000 reported stem cell transplants worldwide
  - Efficacy reported in Severe systemic sclerosis and juvenile sclerosis, MS, SLE, juvenile idiopathic arthritis, multiple sclerosis, NMO and others

- Durable (>3 year) complete remissions off therapy occurred in large numbers of patients\textsuperscript{3,4}
  - 23-71%
  - Suggests curative potential by resetting the immune system

1. Ramalingam and Shah (2021), Stem cell therapy as a Treatment for Autoimmune Disease, \textit{Current Allergy and Asthma Reports}
Systemic Lympho-ablation is Potentially Curative, but Toxic

A series of randomized controlled studies have been conducted to test lympho-ablation followed by stem cell rescue for refractory autoimmune disease\textsuperscript{1,2}

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- 23-71%
- Suggests curative potential by resetting the immune system

Toxicity was unacceptable with high intensity* lympho-ablative regimens (11% mortality)

- *Containing TBI or high dose busulfan

Reduced toxicity with intermediate conditioning** regimens, while maintaining efficacy

- **Utilizing cyclophosphamide with anti-thymocyte globulin

\textsuperscript{1} Ramalingam and Shah (2021), Stem cell therapy as a Treatment for Autoimmune Disease, \textit{Current Allergy and Asthma Reports}
\textsuperscript{2} Swart \textit{et al} (2017), Haematopoietic stem cell transplantation for autoimmune disease, \textit{Nature Reviews}
\textsuperscript{3} Sullivan \textit{et al} (2009), Hematopoietic cell transplantation for autoimmune disease, \textit{Biol Blood Marrow Transplant}
\textsuperscript{4} Farge \textit{et al} (2010), Autologous hematopoietic stem cell transplantation for autoimmune diseases, \textit{Haematologica}
What We Know…. (a brief summary)

• Autoimmune disease is a major global unmet need
• B cells play a central role in the many autoimmune diseases
• Antibody mediated clearance of B cells is incomplete and without durable responses
• Many autoimmune disease may be “cured” with deep lympho-ablation
  • Toxicity of deep lympho-ablation severely limits use of stem cell transplant

**Engineered T cells (in Oncology):**
• Can traffic through all tissues to effect cytotoxicity
• Have established clinical efficacy for the systemic eradication of B cells
• Can be administered without the toxicity related to deep lymphoablative preconditioning
CD19 CAR-T therapy for autoimmune disease

In the past two years, several papers have shown CD19 CAR-T efficacy in autoimmune disease

3. Muller et. al (2023) CD19-targeted CAR T cells in refractory antisynthetase syndrome, *The Lancet*
Anti-CD19 CAR-T in SLE

Patient treatment schema overview from FAU compassionate use protocol

1. Maschan et al. (2021), Multiple site place-of-care manufactured anti-CD19 CAR-T cells induce high remission rates in B-cell malignancy patients, Nature Communications
Robust T cell expansion observed post-infusion

Similar kinetics as observed with CD19 CAR T-cell therapy in hematologic malignancies

Specific CD19$^+$ B cell aplasia observed for 30 days post-infusion
Rapid recovery of non-B cell leukocyte populations post-lymphodepletion

Remission or near complete remission observed at 3 months

Selected clinical biomarkers change dramatically by 3 months

Reduction observed in SLE associated antibodies

Most patients show a decrease following CAR-T infusion – patient #4 appears to be an outlier

**Nucleosome**

**Sm(D3)**

1. Internal data generated at Cabaletta in collaboration with FAU
Reduction observed in SLE associated antibodies

Patient #4 continues to remain an outlier

1. Internal data generated at Cabaletta in collaboration with FAU
Preservation of pre-infusion vaccine antibodies

Representative titers shown: most patients remain stable or have minimal changes pre/post-infusion

Tetanus

Diphtheria

1. Internal data generated at Cabaletta in collaboration with FAU
Many markers of systemic inflammation decreased at 3 months

B cell cytopenia could drive drop in IL-6 and TNFα either through direct secretion or via T cell activation

1. Internal data generated at Cabaletta in collaboration with FAU
CD19+ B cell recovery observed within 150 days post-infusion

Naïve B cells are the predominant population returning to the periphery post-infusion

Takeaways from initial exploration of CD19 CAR-T in SLE

CD19 41BBz CAR-T appears to have promising efficacy and safety in refractory SLE

• Safety
  • No CRS > grade 1 reported across 5 patients
  • No ICANs of any grade reported
  • Non-B cell cytopenias appear to be due to cyclophosphamide and fludarabine < 14 to 21 days
  • Vaccine and infectious disease antibodies are largely intact

• Efficacy
  • All patients experienced complete or near-complete remission by 3 months
  • No relapses to date: duration of remission has lasted ~ 1 to 2 years (data shared at ACR last Nov)
  • Patients currently off all other immune suppressive therapies
  • Preliminary evidence suggests immune reset across most patients
Active clinical trials exploring CAR-T in autoimmune disease

List below includes CD19 and BCMA CAR-T approaches (search date of 4.21.2023)
Unique considerations for CAR-T in autoimmune disease

Safety, Efficacy, Manufacturing considerations (not exhaustive)
Potential mitigation strategies
Not exhaustive
### Summary

CD19 (FMC63) 41BBz CAR-T for SLE (in FAU compassionate use protocol)

- **B cells are a major driver of autoimmune disease**
  - Antibody secreting function
  - As an antigen presenting cell
    - Secretes pro-inflammatory cytokines as an APC
- **CD19 CAR T-cells have been observed to eliminate all B cells in SLE patients**
  - Superior penetrance as compared to standard biologics approaches
  - Can provide safe and durable complete responses up to two years so far
- **Unique considerations in employing CD19 CAR T-cells in autoimmune disease**
  - Mitigation strategies exist for potential roadblocks
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