Autoimmune Connective Tissue Disease Research Group

Therapeutics

TARGET-DLE

(TARGeted therapy using intra-dermal injection of ETanercept for remission induction in Discoid Lupus Erythematosus)

This NIHR funded clinical trial tests the novel approach of intralesional anti-TNF therapy for discoid lupus erythematosus. DLE causes severe scarring on the face or scalp but we previously showed that it is less responsive to B cell targeted biologics than other SLE manifestations.

ROOTS

(Rituximab Objective Outcomes Trial in SLE)

This NIHR funded clinical trial explores new approaches to evaluation of therapies in SLE aiming to develop a more effective clinical trial design. Patients who primarily have skin and musculoskeletal disease are recruited and studies using a range of detailed objective outcome measures with a lower-dose glucocorticoid comparator arm.

Novel Biomarkers

We have published extensively in the use of B cell flow cytometry to predict response and relapse using B cell depleting therapy, as well as generating novel treatment algorithms. In our current research, we are validating our existing results to lead to new treatment pathways and investigating novel B cell phenotypes. We provide a central B cell monitoring service to 3 multi-centre clinical trials. Our data have been used in industry collaborations to assess new B cell targeted biologics. We have developed novel, improved assays for Type I interferon activity using gene expression and cell specific protein markers.

Regulation of type I interferons

Type I interferons -predominantly produced by plasmacytoid dendritic cells (pDCs)- are crucial mediators of antiviral immunity linking innate and adaptive immune responses. The majority of patients with SLE presents an increased expression of interferon-stimulated genes (ISGs) in their peripheral blood indicating that type I interferon axis is critically implicated in the development of SLE. We currently investigate the key role of pDCs in autoimmunity and how type I interferon system is regulated in patients with SLE.

Musculoskeletal Lupus Erythematosus

Musculoskeletal manifestations are the most common feature of SLE, the most common reason for inclusion into clinical trials, and one of the most important factors determining long term quality of life. Arthritis and other features of lupus are difficult to diagnose and therefore treat. We used ultrasound as a more objective measurement of disease activity and showed that joint and tendon inflammation is much more common than previously thought, which may explain why patient experience is poor. Our next study is a multicentre prospective trial to test whether ultrasound could be used to identify patients who will respond to therapy, and whether it is a useful outcome measure in clinical trials.

Cutaneous Lupus Erythematosus (CLE)

Cutaneous lupus is the other most common manifestation and is also difficult to treat. Many common types of cutaneous lupus seem to be unresponsive to B cell targeted therapies, which is unexplained. In our current research we are using tissue and blood studies in multicentre studies to predict response to conventional and biological therapies.

Cutaneous lupus may result in either a scarring or non-scarring outcome. Once the tissue has scarred, there is no treatment to reverse this process. Furthermore, prevention of scarring is difficult, even in those diagnosed early. Our research focuses on identification of key differences between CLE inflammation that develops into scars and those that heal normally. We aim to deliver suggestions for scar prevention strategies as a result of this research project.

Related Autoimmune Connective Tissue Diseases

Lupus is part of a spectrum of connective tissue diseases including Sjogren's Syndrome, inflammatory myositis, mixed and undifferentiated connective disease. These conditions all share common clinical and immunological features. We are researching ways to classify patients according to their individual clinical and immunological features rather than existing disease criteria.

ANCA Vasculitis

The treatment of ANCA vasculitis has been revolutionised with the use of rituximab, but the best long term use of this therapy is unclear. Frequent therapy can lead to high risk of infection, but too little therapy may allow dangerous flares of disease. We are working on the use of B cell biomarkers to direct ideal time of retreatment with minimal risk of infection.

At-Risk Connective Tissue Disease

ANA is positive years before symptoms of connective tissue disease but in many patients the diagnosis may not be confirmed or refuted immediately, so they are followed up for 12 months or longer until until symptoms resolve or develop into SLE. Delay in diagnosis risks severe flares of disease and higher dose glucocorticoids while tests that identify patients who will progress to SLE could have early intervention for disease prevention. We have a programme of research to prospectively study patients at risk of connective tissue diseases.

People

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Funding

2014-2019	National Institute of Health Research £1m: Improving the evaluation and implementation of biologic therapies in Systemic Lupus Erythematosus
2014-2017	Roche £85,452: Clinical predictors of response to rituximab therapy: a synthesis of Roche clinical trial data
2013-2016	Academy of Medical Sciences £29,072: Understanding cutaneous response to rituximab in systemic lupus erythematosus
2015-2017	Lupus UK £57,832: Ultrasound for Evaluation of Musculoskeletal Lupus
2015-2019	Medical Research Council £5.1m: MASTERPLANS (Workstream 2)
2016-2018	Lupus UK £36,010: Identification of "targets" to prevent scarring outcome in cutaneous Lupus
2016-2017	Medical Research Council £58,000: Prediction of Systemic Lupus Erythematosus in at-risk individuals using a novel type I interferon biomarker
2016-2019	AstraZeneca £250,000: Immunophenotyping Connective Tissue Disease for Optimal Use of Interferon-Targeted Therapies

Key Publications

1. Care MA, Stephenson SJ, Barnes NA, Fan I, Zougman A, El-Sherbiny YM, Vital EM, Westhead DR, Tooze RM, Doody GM. Network Analysis Identifies Proinflammatory Plasma Cell Polarization for Secretion of ISG15 in Human Autoimmunity. J Immunol. 2016 Aug 15;197(4):1447-59.
2. Zayat AS, Md Yusof MY, Wakefield RJ, Conaghan PG, Emery P, Vital EM. The role of ultrasound in assessing musculoskeletal symptoms of systemic lupus erythematosus: a systematic literature review. Rheumatology (Oxford). 2016 Mar;55(3):485-94.
3. Alase AA, El-Sherbiny YM, Vital EM, Turner NA, Wittmann M. IFNλ Stimulates MxA Production in Human Dermal Fibroblasts via a MAPK-Dependent STAT1-Independent Mechanism. J Invest Dermatol. 2015 Dec;135(12):2935-43.
4. Md Yusof MY, Vital EM, Das S, Dass S, Arumugakani G, Savic S, Rawstron AC, Emery P. Repeat cycles of rituximab on clinical relapse in ANCA-associated vasculitis: identifying B cell biomarkers for relapse to guide retreatment decisions. Ann Rheum Dis. 2015 Sep;74(9):1734-8.
5. Vital EM, Wittmann M, Edward S, Yusof Y, MacIver H, Pease CT, Goodfield M, Emery P. Responses to rituximab suggest B cell-independent inflammation in systemic lupus erythematosus. Arthritis Rheumatol. 2015 Jun;67(6):1586-91