

Immune suppression in Systemic Sclerosis: Past, Present and Future

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Systemic sclerosis (SSc) is a connective tissue disease characterized by inflammation and abnormalities of the immune system and of blood vessels, which lead to excessive formation of scar tissue in skin and internal organs. It may therefore come somewhat as a surprise that few clinical trials have convincingly demonstrated any beneficial effects of medication that suppresses the immune system.

The chemotherapeutic drug cyclophosphamide proved effective in slowing down lung disease and reducing skin thickening in the North American Scleroderma Lung Study, but its benefit on lung function waned after discontinuation of the drug. Methotrexate has been recommended for the use in diffuse cutaneous SSc (the subset characterized by generalized skin thickening) based on modest effects on skin thickening, but no effect on organ involvement has been shown. Prednisolone at low doses and azathioprine are commonly used for inflammatory manifestations in muscles and lungs, but high doses of prednisolone are not recommended because of potential ill effects on kidney function. Mycophenolate is currently under investigation for SSc lung disease.

Recent studies have shown that much higher doses of immune-suppressive medication may be more effective when combined with stem cell transplantation. The North American SCOT-trial and European ASTIS-trial will compare safety and efficacy of this new treatment modality with pulse-therapy cyclophosphamide. Long-term follow up of patients is needed to determine whether stem cell transplantation confers a survival benefit.

The advent of 'biologicals' (new biotech products) has opened new avenues for targeted treatment of connective tissue diseases including SSc. Small clinical (non-controlled) studies have been conducted with infliximab, antithymocyte globulin, and rituximab, with varying results, however.

It remains to be seen that blockade of a single pro-inflammatory mediator or depletion of one immune cell subset is sufficient to alter the course of a complex disease such as SSc. Recent gene expression studies on skin specimens from SSc patients with common clinical features have confirmed that SSc is a heterogeneous disease.

So far, the disease course is difficult to predict in individual patients on the basis of clinical and laboratory characteristics. Large well-designed trials in defined subgroups of patients, e.g. those with clear signs of inflammation, are needed to demonstrate the benefits of new immunosuppressive medication.

Immune suppression i systemisk sklerose: Fortid, Nutid og fremtid

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Systemisk sklerose (SSC) er en bindevævssygdom karakteriseret ved betændelse og deformiteter i immunsystemet og i blodkar, som fører til overdreven dannelse af arvæv i hud og indre organer. Det

kan derfor komme lidt som en overraskelse, at få kliniske studier overbevisende har vist en gavnlig effekt af medicin, der undertrykker immunsystemet.

De kemoterapeutiske stoffer cyclophosphamid vist sig effektiv i at bremse lungesygdom og reduktion af hud fortykkes i de nordamerikanske Scleroderma Lung Study, men dens ydelse på lungefunktion aftog efter seponering af lægemidlet. Methotrexat, har været anbefalet til brug i diffus kutan SSC (den delmængde karakteriseret ved generaliseret huden fortykkelse), baseret på beskedne virkninger på huden bliver tykkere, men ingen effekt på orgel engagement er blevet vist. Prednisolon ved lave doser og azathioprin er almindeligt anvendt til inflammatoriske manifestationer i muskler og lunger, men høje doser af prednisolon kan ikke anbefales på grund af potentielle skadelige virkninger på nyrefunktionen. Mycophenolatmofetil i øjeblikket er under efterforskning for SSC lungesygdom.

Nylige undersøgelser har vist, at meget højere doser af immun-undertrykkende medicin kan være mere effektive, når det kombineres med stamcelletransplantation. De nordamerikanske SCOT-forsøg og europæiske Astis-forsøg vil sammenligne sikkerhed og effekt af denne nye behandlingsmetode med puls-terapi cyclophosphamid. Langsigtet opfølgning af patienter, der er nødvendig for at afgøre, om stamcelletransplantation medfører en forøget overlevelse.

Fremkomsten af 'Biologicals' (ny bioteknologiske produkter) har åbnet nye muligheder for målrettet behandling af bindevævssygdomme herunder SSC. Små kliniske (ikke-kontrollerede) undersøgelser er udført med infliximab, antithymocyt globulin, og rituximab, med varierende resultater, dog.

Det er stadig uvist, at blokaden af et enkelt pro-inflammatorisk mediator eller udtynding af en immun celle delmængde er tilstrækkelig til at ændre kursen i en kompleks sygdom som SSC. Nylige genekspression studier på huden prøver fra VSK patienter med fælles kliniske funktioner har bekræftet, at SSC er en heterogen sygdom.

Hidtil har sygdommen naturligvis er vanskeligt at forudsige den enkelte patients på grundlag af kliniske og laboratoriemæssige karakteristika. Store veldesignede forsøg i afgrænsede undergrupper af patienter, fx dem med tydelige tegn på betændelse, er nødvendige for at påvise fordelene ved nye immundæmpende medicin.