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Treatment options for chronic mucocutaneous candidiasis

Frank L. van de Veerdonk [a,b,*], Mihai G. Netea [a,b]

[a] Department of Internal Medicine, Radboud University Medical Center, Nijmegen, The Netherlands
[b] Radboud Center for Infectious Diseases (RCI), The Netherlands

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Summary Autosomal dominant chronic mucocutaneous candidiasis (AD-CMC) is a rare and severe primary immunodeficiency that is characterized by mucocutaneous fungal infection, autoimmunity, cerebral aneurysms, and oropharyngeal and esophageal cancer. Recently, it was discovered that *STAT1* mutations are responsible for AD-CMC. These mutations lead to the inability of STAT1 to be dephosphorylated, resulting in hyperphosphorylation, increased binding to the DNA, and gain of function (GOF) effects on STAT1 signaling. Furthermore, a characteristic feature of AD-CMC patients is deficiency in the T-helper 17 (Th17) responses, which is believed to be the immunological cause of the mucocutaneous fungal infection. No targeted treatment other than lifelong antifungal prophylaxis exists for AD-CMC. However, the discovery of the genetic and immunological defects makes it now possible to explore new treatment strategies. This review will discuss immunomodulatory treatment options that can be explored in patients with *STAT1* GOF mutations.

Introduction

Autosomal dominant chronic mucocutaneous candidiasis (AD-CMC; OMIM#614162 orphan designation ORPHA1334) is a rare and severe primary immunodeficiency. AD-CMC leads to a significant decrease of life expectancy and has a large impact on the quality of life of the patient. The hallmark of AD-CMC is severe mucocutaneous fungal infection with predominantly *Candida albicans*; however, autoimmune phenomena, cerebral aneurysms, and oropharyngeal and esophageal cancer have also been associated with this disease.[1–3] Although CMC had been known as an autosomal dominant disease for many years, its genetic cause remained unclear for a long time. Heterozygous mutations in the signal transducer and activator of transcription 1 (*STAT1*) gene were found to be responsible for AD-CMC.[1,2] In contrast to the loss-of-function mutations of *STAT1* that were already described to be associated with viral and mycobacterial infections, *STAT1* mutations that cause AD-CMC are gain-of-function (GOF) mutations.[2,4,5] *STAT1* GOF mutations can also lead to invasive endemic mycosis (such as disseminated coccidioidomycosis and histoplasmosis), viral infections, IPEX (Immunodysregulation Polyendocrinopathy Enteropathy X-linked) -like syndrome and a form of a fatal combined immunodeficiency.[3,6–8] This highlights

* Corresponding author. Department of Internal Medicine (463), Radboud University Nijmegen Medical Center, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands. Tel.: +31 24 3618819; fax: +31 24 3541734.
E-mail address: frank.vandeveerdonk@radboudumc.nl (F.L. van de Veerdonk).

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the significant disease impact of these rare mutations and the need to explore novel treatment strategies.

STAT1 GOF mutations lead to characteristic immunological functional defects such as hyperphosphorylation of STAT1 molecules that accumulate in the nucleus.[2,4] This increased phosphorylation results in a gain of function of STAT1 signaling. Following the transfection of STAT1-deficient fibrosarcoma cells with these alleles, the response to cytokines (especially interferons) that bind receptors that induce STAT1 signaling was increased compared to control cells, in terms of STAT1 phosphorylation, GAS-binding activity, reporter gene induction, and the induction of endogenous target genes.[2] This characteristic defect in dephosphorylation of STAT1 results in a specific immunological defect in the development of T helper 17 (Th17) cells, presumably due to the inhibitory effects induced by interferons on Th17. The Th17 defect explains in turn the increased susceptibility to mucosal fungal infections,[1,2] due to the essential role of Th17-derived cytokines for neutrophil recruitment to the site of infection.[9] In line with this, patients with hyper IgE syndrome, which is a primary immunodeficiency that is characterized by CMC, have mutations in *STAT3*, which is crucial for Th17 development as well.[10] Patients with an autoimmune syndrome called Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy (APECED) who suffer from autoimmune diseases as a result of an *AIRE* gene mutation also suffer from CMC. These patients were found to have high concentrations of neutralizing autoantibodies specifically directed against the Th17 cytokines (IL-17A, IL-17F and IL-22), explaining the CMC in the context of their autoimmune disease.[11,12] Consistent with this hypothesis, genetic predisposition to CMC was shown to be due to a specific hypomorphic heterozygous mutation in *IL17F* in a kindred with AD-CMC, and due to a biallelic amorphic mutation of *IL17RA* in a kindred with autosomal recessive CMC,[13] demonstrating that defective IL-17 signaling is responsible for the chronic mucocutaneous candidiasis seen in AD-CMC.

First immunomodulatory interventions explored in CMC

Charles Kirkpatrick et al. reported the first immunomodulatory treatment options in CMC.[14,15] They described in 1970 that infusion of donor lymphocytes ameliorated fungal infection for a time-period of 8 months.[14] In addition, they demonstrated that the fungal infection of the skin (but not the nails) could be ameliorated with "transfer factor", which is an extract obtained from sensitized donor lymphocytes.[15] These studies already highlighted the importance of lymphocyte function in the protection against mucocutaneous fungal infections observed in CMC and were the first to explore its potential for therapeutic use in CMC.

Granulocyte colony stimulating factors for the treatment of CMC

Shahar et al. reported a patient with CMC, later confirmed to have a *STAT1* GOF mutation, displaying low percentages of monocytes, a defective LPS-induced IL-1 production by monocytes, and defective neutrophil recruitment in response to zymosan.[16] This patient was treated with granulocyte macrophage colony stimulating factor (GM-CSF), which resulted in a beneficial clinical response.[16] Three years later, the patient was treated with G-CSF, which resulted in a similar control of the disease. When G-CSF was stopped fungal disease developed again, which was accompanied with a defective Th17 response in-vitro.[17] When G-CSF was administered, fungal infection was controlled again and defective Th17 responses were restored within a time period of four weeks.[17] While this report was promising, a subsequent study showed that two patients suffering from CMC due to *STAT1* GOF mutation did not respond to a four-week course of G-CSF.[18] Important to note is that GM-CSF has also been reported to be of clinical benefit for patients with CARD9 (Caspase-Associated Recruitment Domain 9) deficiency, which can also present with CMC.[19] These data suggest that in some circumstances CSFs can be beneficial in the treatment of CMC, however a prospective clinical trial is needed to evaluate whether and which patients with CMC might benefit from this treatment strategy.

Inhibition of cytokines blocking Th17 responses

STAT1 GOF mutations result in increased STAT1 DNA binding and target gene transcription activity upon stimulation with various cytokines, including IFN-γ, IFN-α, and IL-27.[2] One hypothesis why patients with CMC have defective Th17 responses is that *STAT1* GOF result in exaggerated signals induced by cytokines, such as IFNγ and IL-27, which inhibit the development of Th17 cells.[20,21] Therefore, a potential therapeutic strategy would be to inhibit the signaling of these cytokines to prevent their inhibitory function on Th17 development. IFNγ and IL-27 are dependent on both JAK1 and JAK2 to induce intracellular signaling. Interestingly, a recent study reported that the use of the JAK1/JAK2 inhibitor ruxolitinib was successful in the treatment of fungal infection in a patient with *STAT1* GOF mutation.[22] This is so far the only report on this adjunctive therapy, and it remains to be investigated whether this beneficial response can be observed in other patients with a *STAT1* GOF mutation. However, it is important to be aware that the cytokine IL-23, which is important for optimal IL-17 and IL-22 responses, is also dependent on JAK2, and drugs such as ruxolitinib could therefore also have detrimental effects in AD-CMC.[23]

Histone deacetylase (HDAC) inhibitors

STAT molecules are essential for regulating responses to inflammation and infection. STAT1 and STAT3 play opposing roles in most cell types and the exact mechanisms explaining these opposing roles still remain to be elucidated. This could be for example due to competition for common receptor docking sites or to an altered nuclear transport.[24] STAT1 activity is dependent on phosphorylation in the cytoplasm by tyrosine kinases, which allows its translocation into the nucleus. To recycle STAT1 back to the cytoplasm it has to be dephosphorylated by phosphatases, such as T-

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