ANCA-associated vasculitis: The ADVOCATE Study
Avacopan, a selective C5a receptor antagonist, effective in ANCA-vasculitis

ABSTRACT: ANCA-associated vasculitis causes inflammation of small blood vessels, which may result in severe injury to the kidneys, lungs and other organs – even death. Immunosuppressive therapies save patients, but in many cases the side effects cannot be ignored. Avacopan, a novel substance, has shown promise in this regard in a Phase III study that was presented at the ERA-EDTA Congress today.

ANCA-associated vasculitis (AAV) is a systemic disease involving the formation of special autoantibodies (so-called anti-neutrophil cytoplasmic antibodies/ANCA) and vascular inflammation. There are several diseases associated with involvement of the kidneys, lungs, upper respiratory tract, heart, skin and the nervous system; potentially life-threatening courses of disease are also possible. Immunosuppressive therapy is provided, which can lead to infections as a known side effect, among others. Modern immunosuppressants (e.g. rituximab, an anti-CD20 monoclonal antibody) do not block the entire immune system as corticoids, for example, do, but only parts of it, so other pathways of the immune system continue to work.

A role in AAV pathogenesis is also played by the complement system of the immune system, especially complement factor C5a. Neutrophil leukocytes have immunostimulating C5a receptors (C5aR). Avacopan (formerly CCX168) is an orally...
selective C5aR antagonist that inhibits C5a-induced activation of immune cells and thus AAV – as already demonstrated in two clinical Phase II trials.

The phase III ADVOCATE trial evaluated the safety and efficacy of avacopan – also with regard to lower doses of glucocorticoids being needed with avacopan. Patients were randomized 1:1 and received, over a total of 52 weeks, either the glucocorticoid prednisone (n=164) or avacopan (n=166) in combination with a) cyclophosphamide (oral or intravenous) followed by azathioprine or b) four infusions of rituximab (RTX). Patients were stratified on the basis of treatment (RTX i.v., or orally administered cyclophosphamide), the specific type of ANCA and newly diagnosed or relapsing AAV disease. Response to treatment (remission, primary endpoint) was defined as BVAS=0 (disease activity according to the “Birmingham Vasculitis Activity Score”) plus prednisone tapering (at least four weeks before week 26). Sustained remission was present if there was no relapse from week 26 to 52.

At Week 26, 72.3% subjects achieved remission in the avacopan compared to 70.1% in the prednisone group (p<0.0001 for non-inferiority). At Week 52, 65.7% subjects achieved sustained remission in the avacopan compared to 54.9% in the prednisone group achieving both non-inferiority and superiority to prednisone group (p=0.0066 for superiority of avacopan).

”AAV must be treated with immunosuppressants. However, the side effects of these substances can be severe – especially at higher corticosteroid doses”, explains Professor David Jayne, Cambridge. “With avacopan, a drug that could be available in the future a reduction in corticoid use and to more sustained remission is achieved– in the trial, at least 10% more patients were still in remission after one year. The benefit of avacopan in patients with renal involvement was remarkable and it was well-tolerated.”

“Research is developing increasingly well-targeted immunosuppressive or immunomodulatory drugs for many areas of medicine”, adds Maria Jose Soler Romeo, Chair of the Paper Selection Committee of the 2020 ERA-EDTA Congress. “This is so important, because potentially life-threatening diseases such as AAV often require treatments that themselves pose risks – new immunosuppressive, specifically targeting substances are therefore urgently needed in order to improve therapies further and avoid the high dose steroids side effects.”

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