ANCA-associated vasculitis is now associated with a new outlook.

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ANCA-ASSOCIATED VASCULITIS

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Understanding ANCA-associated vasculitis.

ANCA-associated vasculitis is a heterogeneous group of rare, life-threatening, systemic autoimmune diseases that are characterized by necrotizing vasculitis that predominantly affects the small to medium-sized blood vessels.[1-4]

The group is[1,3]:

- Granulomatosis with polyangiitis (GPA)
- Microscopic polyangiitis (MPA)
- Eosinophilic granulomatosis with polyangiitis (EGPA)

ANCA-associated vasculitis is shown to impair patients' physical, financial, and emotional quality of life.[5-10]

Despite implementation of the standard of care, frequent relapses can:

- Result in permanent and cumulative organ damage (renal and cardiovascular-related issues are most common)[11,12]
- Lead to procedures like bronchoscopy, biopsy, dialysis, plasma exchange, and hospitalization[13]
- Contribute to impaired Health-Related Quality of Life (HRQoL) presenting with high levels of fatigue and impaired physical and mental functioning[5-7]
- Financially impact patients—in one study 26% of patients reported unemployment due to ill health[8-10]

A combination of broad immunosuppressant agents and high-dose glucocorticoids are used to achieve remission.

Once achieved, modified immunosuppressive maintenance treatment is used for preventing relapse. However, these options may not meet treatment goals due to[14,15]:

- **Frequent relapse**—Relapse rates vary based on the type of maintenance treatment a patient is receiving. A 2019 study investigated the relapse rates of rituximab vs azathioprine and found that 13% to 38% of patients experienced relapse within 20 months, despite continued immunosuppression[16]
- **High risk of severe infection**—In a recent Swedish study, 38.4% of patients required hospitalization in the first 6 months after diagnosis and induction of therapy for remission[17]
- **Significant toxicity**—While seeking to maximize treatment outcomes, current treatment options may lead to adverse reactions and toxicities. Furthermore, the longer a patient is exposed, the more pronounced the adverse effects may become[12]

ANCA-associated vasculitis: unraveling the pathogenesis.

There are 4 key steps in the development of ANCA-associated vasculitis.

1 Loss of immune tolerance and ANCA development [2,18]

Anti-neutrophil cytoplasmic autoantibodies (ANCA) are most commonly directed against either myeloperoxidase (MPO) or serine proteinase 3 (PR3), which are granular proteins normally located within neutrophils.

2 Neutrophil priming [2]

Neutrophils are primed (partially activated) by a combination of factors, including the inflammatory milieu of cytokines produced in response to an infection or another event. This results in the exposure of PR3 and MPO on the neutrophil surface.

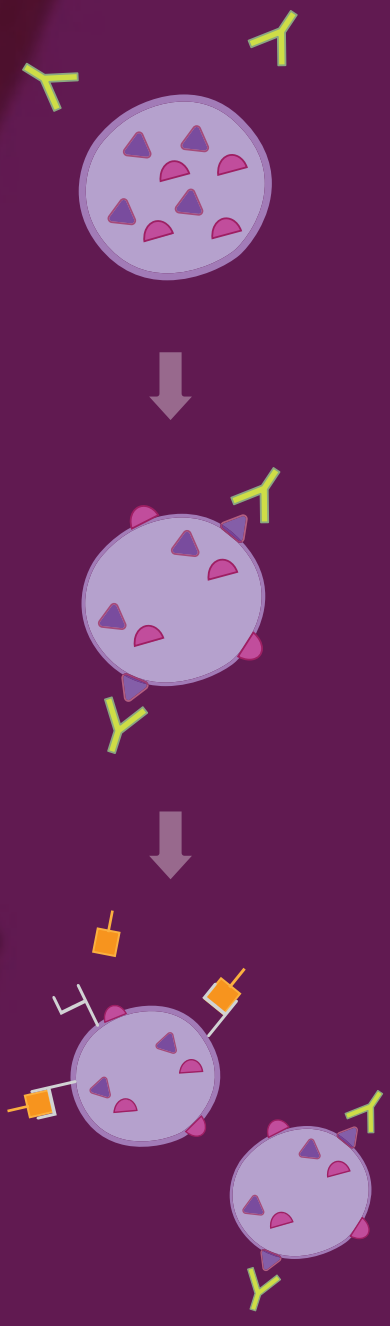
3 Activation of neutrophils [3,15]

ANCA binding leads to the generation of the complement fragment known as C5a.

When C5a binds to the C5a receptor (C5aR) on neutrophils, they release destructive mediators that chronically inflame and eventually destroy vascular tissues and the organs fed by those blood vessels.

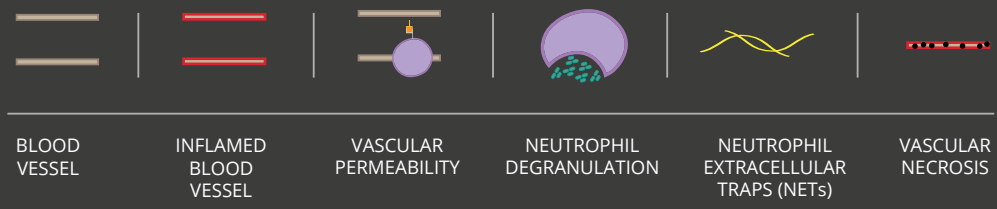
4 Complement amplification [2,3]

Further activation of the complement pathway leads to tissue damage and the clinical manifestations of ANCA-associated vasculitis.



The complement system:
paving the way for new possibilities.

The complement system plays a key role in ANCA-associated vasculitis.



C5a—a potent pro-inflammatory mediator [2,3]

A major downstream effector molecule in the alternative complement pathway, C5a primes and activates neutrophils, and functions as a strong chemoattractant.

Neutrophils are primed and activated [2,3,19]

Primed neutrophils stick to blood vessels at the site of inflammation.

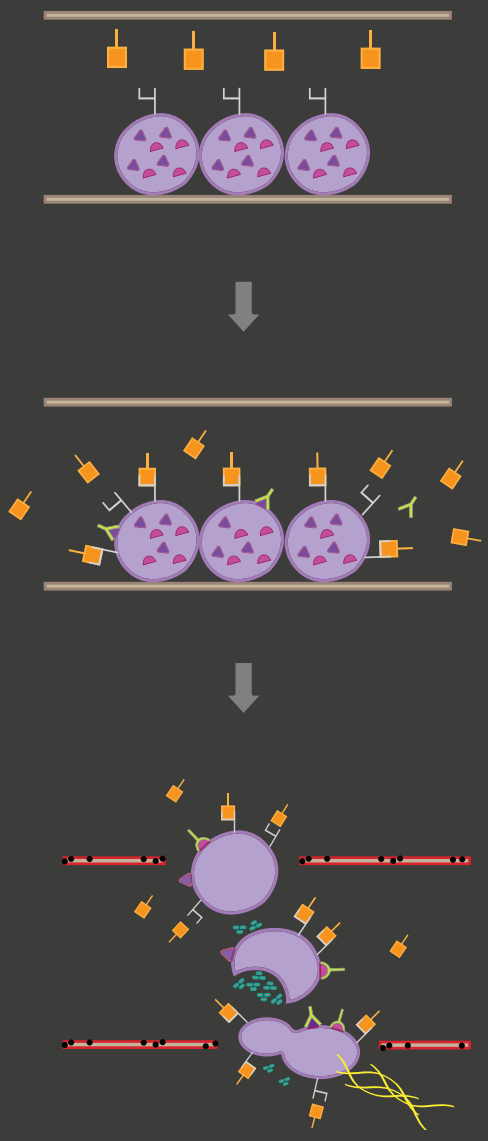
The complement system is activated by an inflammatory environment where cytokines are released in response to an infection or other insult.

C5a is generated in and around the site where the primed neutrophils are sticking and activates them by binding to C5aR.

Vicious amplification loop [2,3]

C5a-C5aR-mediated neutrophil activation leads to the attraction of more neutrophils to the inflammatory site, and drives neutrophils to degranulate, releasing toxic lysosomal proteases and oxidative free radicals. Additionally, these neutrophils produce NETs which intensify the inflammatory process at the vascular injury site.

The vicious feedback loop driven by the complement system eventually leads to chronic vasculitis, vascular permeability, vascular necrosis, and ultimately organ damage.



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