Pediatric ANCA-Associated Vasculitis: Current Evidence and Therapeutic Landscape

Complement inhibition represents the most significant therapeutic advance

Pharmacological mechanisms and rationale for complement inhibition

Avacopan transforms ANCAv treatment by targeting the inflammatory amplification loop central to disease pathogenesis (1). As an oral C5a receptor (C5aR/CD88) antagonist, avacopan selectively blocks C5a binding to C5aR1, preventing C5a-mediated neutrophil activation and chemotaxis while preserving beneficial complement functions. The drug interrupts a vicious cycle where ANCA-activated neutrophils degranulate, activate the alternative complement pathway, generate C5a, which then recruits and primes additional neutrophils for ANCA activation.

Experimental evidence strongly supports this approach: C5aR-deficient mice show complete protection from MPO-ANCA-induced glomerulonephritis, while C6-deficient mice (lacking membrane attack complex formation) remain vulnerable, confirming that C5a rather than terminal complement products drives pathogenesis. In humans, elevated plasma levels of C3a, C5a, soluble C5b-9, and factor B correlate with active disease and normalize with remission (2).

The pharmacokinetic profile presents both opportunities and challenges for pediatric application. Avacopan achieves peak concentrations ~2 hours after oral administration, with an elimination half-life of 97.6 hours enabling twice-daily dosing. The drug is highly protein-bound and primarily metabolized by CYP3A4 to an active metabolite (M1), representing potential concerns for pediatric populations given developmental changes in drug metabolism and drug interactions (3). Strong CYP3A4 inhibitors require dose reduction to 30 mg once daily, while inducers should be avoided entirely.

Adult versus pediatric pharmacological considerations

Critical gap: Limited pediatric pharmacokinetic data exists for avacopan or other complement inhibitors in ANCAv (4). Adult studies show no clinically relevant differences across age ranges (18-83 years), sex, race, or body weight (40.3-174 kg), and no dose adjustment is required for mild-to-severe renal impairment. However, developmental changes in CYP3A4 activity, body composition, and organ function in children would likely affect drug disposition significantly.

The FDA label explicitly states that safety and efficacy are "not known in children under 18," and pediatric trials are ongoing (5). This represents a critical regulatory gap given the theoretical advantages of complement inhibition in pediatric populations, where steroid-sparing effects would be particularly valuable for growing children at risk for growth retardation and bone disease from chronic glucocorticoid exposure.

Limited evidence from a single pediatric case report describes successful use of eculizumab (a C5 inhibitor) followed by ravulizumab transition in a 5-year-old with MPO-ANCA vasculitis recurrence post-kidney transplant, providing proof-of-concept for complement inhibition in pediatric ANCAv (6).

Pediatric ANCAv presents with distinct clinical characteristics and worse outcomes

Disease onset and presentation patterns differ significantly

Pediatric ANCAv demonstrates more aggressive disease patterns with higher organ involvement rates and more frequent relapses compared to adult disease (7). Children present at a median age of 11.5-14 years with constitutional symptoms in nearly 100% of cases versus lower rates in adults (8). Renal involvement occurs in 65-78% of pediatric GPA cases compared to 50-65% in adults, and 88-95% of pediatric MPA cases versus 70-85% in adults (9). This higher renal involvement translates to more severe presentations, with 39% experiencing rapidly progressive glomerulonephritis and 25% requiring dialysis at presentation (10).

The ANCA pattern distribution also differs, with MPO-ANCA predominating in pediatric populations (41-72% of cases) compared to more balanced patterns in adults (11). MPO-ANCA pediatric patients are younger at diagnosis (median 13.5 years), predominantly female (92%), and more likely to develop renal-limited disease, while PR3-ANCA patients present older (median 15 years) with more ENT involvement and skin manifestations (12).

ENT manifestations occur more frequently and severely in children (45.7% versus adults), with subglottic stenosis representing a more common complication (13). Pediatric patients show less frequent myalgias and peripheral neuropathy but higher rates of fever, nasal cartilage damage, and ischemic abdominal pain in GPA (14).

Outcomes reveal higher relapse rates but potentially better long-term survival

Pediatric patients experience significantly higher relapse rates—24.5 flares per 100 patient-years compared to 18.7 in adults—but demonstrate more accumulated disease damage at last visit, primarily affecting ENT structures (15). Despite more aggressive disease, children generally show better long-term renal survival than adults, though 20-35% still progress to end-stage renal disease (16).

Treatment patterns reflect these challenges: pediatric patients require longer maintenance therapy periods and are less likely to achieve treatment-free status (15% versus 42% in adults) (17). The higher relapse rates and need for prolonged immunosuppression make steroid-sparing approaches particularly attractive for pediatric populations, where chronic glucocorticoid exposure poses significant risks for growth, bone development, and metabolic complications.

Recent registry data reveals that P-ANCA positivity serves as a potential marker for higher relapse risk specifically in pediatric patients, offering opportunities for risk stratification and treatment intensification in high-risk children (18).

Diagnostic approaches require pediatric-specific adaptations

Current diagnostic methods show limitations in pediatric populations

Diagnosis remains challenging in pediatric ANCAv, with median time to diagnosis of 6-12 months due to atypical presentations and limited pediatric-specific diagnostic criteria (19). Laboratory diagnostics rely on the same ANCA testing methods used in adults, with ELISA preferred over

immunofluorescence for higher specificity (20). MPO-ANCA and PR3-ANCA remain the key biomarkers, though their prognostic value differs in children compared to adults (21).

Tissue biopsy represents the gold standard with 91.5% diagnostic yield in GPA, but fewer than 50% of biopsies show characteristic vasculitic changes (22). Critical clinical decisions often require initiating treatment based on positive ANCA serology and compatible clinical presentation without waiting for biopsy confirmation in rapidly deteriorating patients (23).

Recent breakthrough developments in biomarker research offer promise for improving pediatric diagnosis. Urinary soluble CD163 (usCD163) demonstrates 94% sensitivity and 91% specificity for detecting relapsing ANCA glomerulonephritis, with an area under the ROC curve of 0.96 for identifying renal vasculitis relapse (24). This non-invasive biomarker correlates strongly with histologic activity and normalizes with treatment, potentially reducing the need for repeat kidney biopsies in children (25).

Prevention measures remain limited

Primary prevention measures for ANCA vasculitis are limited (26). Secondary prevention focuses on infection prophylaxis with trimethoprim-sulfamethoxazole for Pneumocystis jirovecii pneumonia during cyclophosphamide courses or following rituximab, annual pneumococcal and influenza vaccinations, and regular monitoring of immunoglobulin G levels with replacement therapy when levels fall below 5 g/L (27).

Treatment options rely heavily on extrapolated adult data

<u>Authorized treatments show significant regulatory gaps</u>

ANCAv treatments for pediatric populations create a treatment landscape dependent on off-label use of adult-approved therapies (28). Rituximab plus glucocorticoids, approved by the FDA in April 2011 for adults with GPA and MPA, represents the most established treatment combination despite lack of pediatric approval. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) consensus accepts both cyclophosphamide and rituximab as primary induction choices, with standardized consensus treatment plans providing guidance for pediatric dosing (29).

Rituximab demonstrates effectiveness across pediatric age groups with 375 mg/m^2 IV weekly for 4 weeks or alternative 1000 mg IV on days 1 and 15 (30). Maintenance therapy typically involves 500 mg infusions every 6 months for 18-24 months, though pediatric patients often require longer maintenance periods given higher relapse rates (31).

Avacopan plus glucocorticoids, approved in October 2021 for adults, explicitly states in its prescribing information that safety and efficacy are under evaluation in children under the age of 18 (32). The ADVOCATE trial demonstrated superior sustained remission at 52 weeks (65.7% versus 54.9% with prednisone) and better renal recovery, particularly in patients with severe renal insufficiency, making it an attractive option for pediatric use (33).

<u>Off-label use patterns reflect clinical needs</u>

Off-label medication use is extensive in pediatric ANCAv treatment, reflecting the absence of pediatric-specific approvals and the need to adapt adult evidence for children (34). Commonly used

off-label medications include rituximab for maintenance therapy beyond standard protocols, mycophenolate mofetil for steroid-sparing maintenance, intravenous immunoglobulin for refractory cases, and plasma exchange for severe renal disease or diffuse alveolar hemorrhage (35).

Treatment protocols from major medical centers follow standardized approaches: the European SHARE Initiative provides minimum standards based on adult-derived recommendations adapted for children, while CARRA consensus treatment plans offer two alternatives each for induction and maintenance therapy (36). Induction typically involves methylprednisolone 1000 mg IV for 1-3 days followed by oral prednisone 1 mg/kg/day with standardized tapering over 5-6 months, combined with either cyclophosphamide or rituximab (37).

Emerging evidence supports reduced glucocorticoid exposure when combined with rituximab, addressing particular concerns about growth impairment and bone disease in developing children (38). The PEXIVAS trial demonstrated that reduced-dose glucocorticoid regimens were non-inferior to standard-dose for major outcomes while significantly reducing serious infections (39).

Recent evidence reveals paradigm shifts and emerging connections

<u>COVID-19 emerges as potential trigger for pediatric ANCAv</u>

Multiple pediatric cases of new-onset ANCAv following COVID-19 infection have emerged, representing a potentially significant epidemiological shift (40). These cases predominantly show PR3-ANCA positivity with severe pulmonary involvement, occurring 2-16 weeks post-COVID-19 infection (41). Proposed mechanisms include molecular mimicry between SARS-CoV-2 and neutrophil proteins, excessive neutrophil extracellular trap (NET) formation triggered by viral infection, and impaired NET clearance in the post-COVID state (42).

This connection has important implications for increased vigilance in post-COVID pediatric patients and potential pandemic-related increases in pediatric ANCAv incidence (43). Treatment response to standard immunosuppressive therapy appears favorable, but long-term follow-up studies are needed to understand the full clinical impact (44).

<u>Breakthrough biomarker developments transform monitoring capabilities</u>

The discovery of urinary soluble CD163 as a highly sensitive and specific biomarker represents a transformative advance for pediatric ANCAv monitoring (45). This biomarker correlates with fibrinoid necrosis ($Rho=0.48$, $p<0.001$) and cellular crescents ($Rho=0.70$, $p<0.001$), levels normalize after treatment, and remain low during stable remission (46). The optimal cut-point of 250 ng/mmol (normalized to urine creatinine) provides clinical-grade diagnostic capability with potential to reduce repeat kidney biopsies in children (47).

Neutrophil extracellular traps (NETs) have emerged as central mediators of tissue damage, independent of ANCA levels (48). NET formation correlates with active disease and provides mechanistic rationale for novel therapeutic targets including DNase I therapy for NET degradation and cathepsin C inhibitors to reduce NET formation (49).

Treatment paradigms shift toward precision medicine approaches

The field is moving from acute treatment models toward chronic disease management with emphasis on long-term quality of life outcomes and minimizing treatment-related toxicity (50). This shift is particularly relevant for pediatric populations given longer life expectancy and greater vulnerability to treatment-related complications.

Recent real-world evidence shows avacopan achieving 90% remission rates, exceeding clinical trial results, with improved tolerability profiles confirmed in post-marketing surveillance (51). The integration of patient-reported outcome measures, glucocorticoid toxicity indices, and long-term organ preservation strategies reflects evolving treatment goals beyond simple remission achievement (52).

Critical research gaps demand urgent attention

Pediatric-specific development needs

The limited pediatric pharmacokinetic data, safety profiles, and efficacy evidence for complement inhibitors represents a critical research gap (53). Age-stratified pharmacokinetic/pharmacodynamic studies, pediatric-appropriate dosing regimens, long-term safety assessments, and dedicated pediatric efficacy trials are urgently needed (54).

Key unknowns include effects on immune development, long-term growth and development impacts, optimal monitoring parameters, and infection risk in immunocompromised children (55). Pediatric case reports with complement inhibition provide encouraging proof-of-concept but cannot substitute for systematic pediatric development programs (56).

Regulatory and guideline limitations

Current regulatory exemptions for orphan drugs limit pediatric study requirements, creating a systematic barrier to pediatric drug development in rare diseases (57). While recent policy changes aim to close pediatric testing loopholes, implementation remains limited for ANCAv treatments (58).

Clinical practice guidelines show minimal pediatric-specific guidance, with KDIGO 2024 and EULAR 2022 updates primarily extrapolating adult recommendations (59). The absence of pediatric-specific treatment algorithms, dosing recommendations, and monitoring protocols creates challenges for optimal care delivery in specialized centers (60).

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