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REVIEW ARTICLE

Aging in Granulomatosis with Polyangiitis and Microscopic Polyangiitis: From Pathophysiology to Clinical Management

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Abstract

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) predominantly affect individuals aged 55–75 years, with granulomatosis with polyangiitis (GPA) being diagnosed most often between 55 and 65 years and microscopic polyangiitis (MPA) between 65 and 75 years. Owing to the general increase in life expectancy, the average age at diagnosis increases, encompassing also those over 75 years old. Unfortunately, the exclusion of these older patients from many clinical trials has limited our understanding of the progression of these diseases in older subjects. The role of immunosenescence and aging in AAV pathogenesis and progression is underexplored, despite potential implications in the understanding of the disease, and potentially for disease management. Although AAV manifestations are largely consistent across age groups, certain features, such as renal involvement and the association with interstitial lung disease, may be more prevalent in older patients. Frailty must be a key consideration in therapeutic decision-making, especially when balancing the efficacy of immunosuppressants with potential side effects. Recent evidence supports the use of rituximab in addition to low-dose glucocorticoids for remission induction in life- or organ-threatening AAV, including in older populations. Furthermore, preliminary evidence supports that avacopan might be as efficient as glucocorticoids in these patients. The immunosuppressive treatment of AAV reduces the immune response to environmental pathogens, with rituximab worsening age-related hypogammaglobulinemia. Thus, prophylactic measures, including vaccination and *Pneumocystis pneumonia* prevention, as well as strategies to mitigate glucocorticoid side effects, should be implemented in AAV management.

1 Introduction

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) are three necrotizing conditions that affect small blood vessels: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg–Strauss syndrome). Over the past five decades, the diagnosis and especially the treatment of these diseases have undergone significant changes, largely owing to the introduction of modern and safer immunosuppressive therapies [1].

While AAV primarily affect patients between 55 and 75 years old, many clinical trials excluded older patients, hindering a comprehensive understanding of the disease across the whole lifespan. For example, in some of the latest

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Key Points

The incidence of ANCA-associated vasculitides (AAV) is higher in older patients, whose clinical presentation is often different with respect to younger patients: fewer ear, nose, and throat (ENT) involvements but more respiratory manifestations.

Frailty assessment is crucial for clinical decision-making about biopsies and stressful treatments.

Rituximab is well tolerated in older patients and remains the preferred options for both induction and maintenance of remission.

randomized trials [2–4], mean ages ranged from 51 to 61 years, thus resulting in scarce evidence for older subjects, limiting our ability to tailor safe and effective management and treatment strategies for older patients with AAV.

The primary objective of this comprehensive review is to present the available data on MPA and GPA in older populations from pathophysiology to management, including adverse effects associated with treatments and discuss strategies to mitigate them.

2 Epidemiology

The overall incidence of AAV (including GPA, MPA, and EGPA) is estimated to be from 0.81 [3] to 3.3 [5–8] per 100.000 inhabitants, with an overall prevalence of up to 42.1 per 100.000 inhabitants [7–9]. Over the last decades, the mean age at diagnosis may have increased, with a rise in the peak age at onset (defined as the age category with the highest incidence rate) from 55–64 years old in the 1980s to over 75 years in the 2000s [7], for both GPA (Table 1, Fig. 1) and MPA (Table 2, Fig. 2). This trend is partially explained by the global aging of the population and the improved healthcare provided to patients older than 75 years.

Significant geographic variations have been noted in subsets of AAV, with a greater prevalence of GPA in Northern Europe, North America, and Canada compared with other regions, and a higher occurrence of MPA in Asia, particularly in Japan than in Europe. However, a similar higher annual incidence of MPA than GPA has also been observed in recent population-based studies from Northern Europe and Minnesota, USA, challenging the paradigm of a higher incidence of GPA in Western countries [6, 10, 11].

3 Immunosenescence and Aging in ANCA-Associated Vasculitis

Immunosenescence is the age-related change of the immune system, resulting from the direct effect of senescence of immune cells and the indirect effect on nonimmune cells. Even though only a few of the biological mechanisms have been clarified, several hallmarks have been defined, including thymic involution, early maturation dysfunctions, disrupted naïve/memory ratio in T and B cells, chronic proinflammatory status ("inflammaging") [12], accumulation of senescent cells with senescence-associated secretory phenotype (SASP), impaired new antigen response, mitochondrial dysfunction, and genomic instability [13, 14].

Immunosenescence contributes to muted vaccination response and increased susceptibility to infections, cardiovascular diseases, obesity, malignancies, and age-related diseases including autoimmunity [15]. However, no studies have been specifically conducted so far in AAV, and therefore the data supporting the contribution of the immune system to aging are clearly overlooked in this disease.

3.1 Innate Immune Senescence

Overall, innate immune senescence is characterized by a reduction in the response to stimuli of the innate immune system (Fig. 3). Among others, senescent macrophages and dendritic cells show a decline in their capability of antigen processing and presentation, as they express fewer major histocompatibility complex (MHC)-II molecules, while their sensitivity to stimuli is diminished owing to the downregulation of Toll-like receptor (TLR) expression and decreased cytokine secretion. This results in a defective response to pathogen-associated molecular patterns (PAMPs) [16, 17]. Monocytes from older individuals show reduced production of interferon (IFN)-α, IFN-γ, interleukin (IL)-1β, C–C motif ligand (CCL)20, and CCL8 and increased expression of C–X3–C motif chemokine receptor 1 (CX3CR1) [18], with an excessive secretion of tumor necrosis factor alpha (TNFα) from immature monocytes contributing to inflammaging [19]. Senescence of natural killer (NK) cells causes a shift from a less mature, cytokine-secreting cluster of differentiation (CD)$14^{+}CD56^{dim}$ subset [20] to a more mature, cytotoxic $CD14^{+}CD56^{bright}$ phenotype, owing to decreased bone marrow precursor production. Additionally, they exhibit reduced cytokine secretion, diminished migration, and altered receptor expression, with upregulation of NKG2D and killer-cell immunoglobulin-like receptor (KIR) and downregulation of NKG2A receptors [21, 22].

The decrease in neutrophil functions, including cytokine signaling, production of peroxide and nitric oxide, and loss

of phagocytic function may contribute to the increased susceptibility to infection in older adults [21, 22]. In healthy patients, senescent neutrophils have a diminished capability of forming neutrophil extracellular traps (NETs), which is associated with increased susceptibility to bacterial colonization in mice [15]. NETosis plays a pivotal role in the pathogenesis of AAV by directly causing endothelial cell damage and vessel inflammation, and indirectly activating the complement system. Nevertheless, the capability of forming NETs in AAV patients has not been compared with that in healthy subjects.

Innate immune senescence is also associated with dysregulation in levels and functionality of the complement system [23]. In healthy subjects, both classical and alternative pathway activities were significantly higher in the older, in contrast to mannose-binding lectin pathway activity. Moreover, C1-inhibitor, C5, C8, and C9 levels increased with age in contrast to a decrease of factor D and C3 levels [23]. Increased complement activity can be immunomodulatory and exacerbate the onset of age-related diseases [24]. In the context of autoimmunity, and particularly in AAV, anaphylatoxins such as C5a play a central role in neutrophil activation, and in general, complement alternative pathway (cAP) activation promotes the inflammation at the endothelial interface [25]. Consequently, C5a receptor antagonists (avacopan) have been developed and recently tested in clinical trials [4, 26]. Given the importance of this pathway in the pathogenesis of AAV, it might be plausible that the age-related dysregulation of the complement system may contribute to AAV occurring more frequently in the older patients.

3.2 Adaptive Immune Senescence

Aging impacts also the T and B cell compartments [27]. Thymic involution plays a crucial role in T cell immunosenescence. Several cross-sectional studies have revealed a peculiar immunological profile of older individuals, characterized by a reduction of the number of circulating naïve $CD4_+$ T cells and T-cell receptor (TCR) diversity [28], and

Table 1 Age at diagnosis of GPA across historical cohorts

References	Inclusion time	Age at diagnosis, mean (SD, if available)	Number of cases	Type of cohort
Andrews, 1990 [124]	1980–1989	61	18	Hospital
Koldingsnes, 2000 [125]	1984–1998	50	55	Population-based
Dadoniene, 2005 [126]	1990–1999	57	10	Population-based
Zeft, 2010 [127]	1993–2006	53 (19)	27	Population-based
Ormerod, 2008 [128]	1995–2004	55	38	Hospital
Catanoso, 2014 [129]	1995–2019	58.8 (20.2)	18	Hospital
Berti, 2017 [6]	1996–2015	56.1 (15.1)	23	Population-based
Mohammad, 2009 [130]	1997–2006	67.6	63	Population-based
Wu, 2015 [131]	1997–2008	49.72 (16.27)	96	National Health Insurance database
Pearce, 2017 [132]	1997–2013	60.0 (15.9)	462	Population-based
Rathman, 2023 [133]	1997–2019	64*	192	Population-based
Reinhold-Keller, 2002 [134]	1998–1998	61	21	Population-based
Reinhold-Keller, 2002 [134]	1998–1998	58	12	Population-based
Reinhold-Keller, 2002 [134]	1999–1999	62	17	Population-based
Reinhold-Keller, 2002 [134]	1999–1999	66	8	Population-based
Nilsen, 2020 [135]	1999–2013	54	88	Population-based
Pierini, 2019 [136]	2000–2015	69.8 (11.3)	19	Hospital
Hissaria, 2008 [137]	2001–2005	56.8 (11.4)	30	Hospital
Pamuk, 2016 [138]	2004–2014	49.8 (13.3)	30	Hospital
Pearce, 2016** [11]	2007–2013	70.2 (58.4–78.6)	107	Population-based
Bataille, 2022 [10]	2010–2017	60.2 (15.6)	1578	Hospital
Kanecki, 2018 [139]	2011–2015	52	1491	Hospital

*Median age

GPA, granulomatosis with polyangiitis; SD, standard deviation

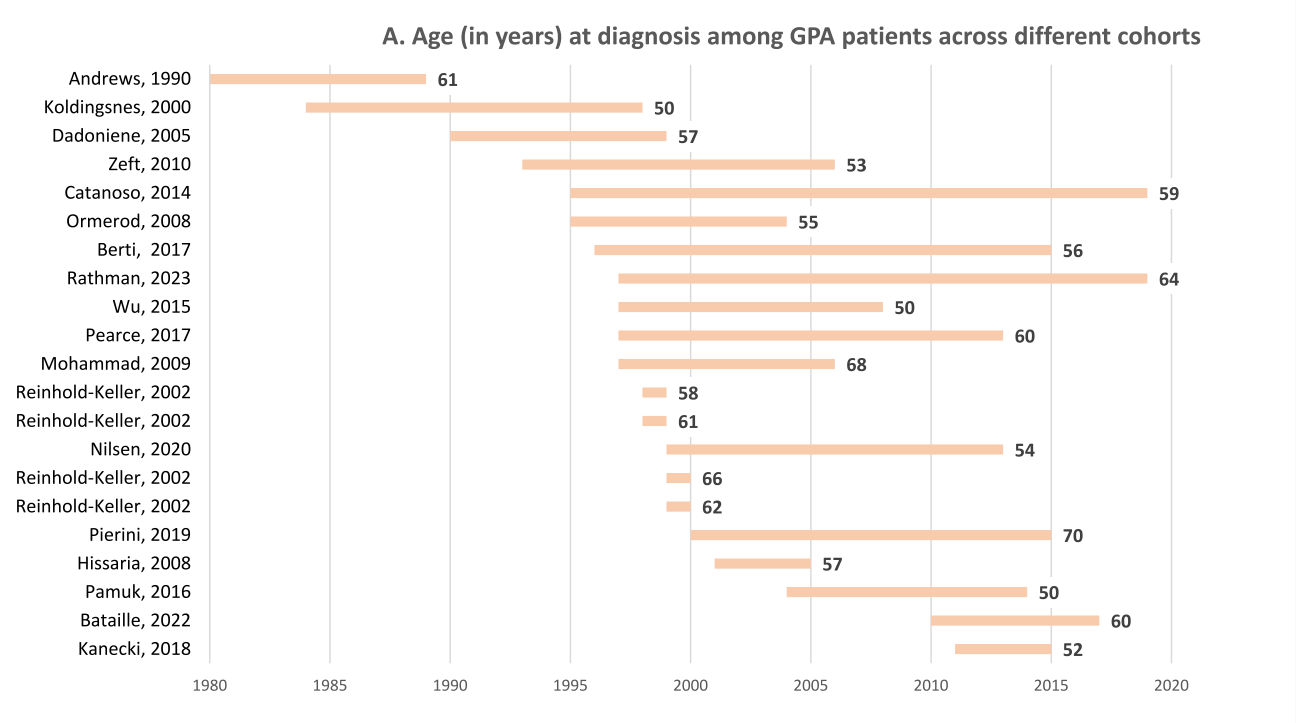

Fig. 1 Age at diagnosis across cohorts over time in GPA. Numbers represent the mean age (in years) at diagnosis of GPA in the different cohorts (references are indexed in Table 1), and the orange bars represent the follow-up duration of the cohorts. GPA, granulomatosis with polyangiitis

Table 2 Age at diagnosis of MPA across historical cohorts

References	Inclusion time	Age at diagnosis, mean (SD, if available)	Number of cases	Type of cohort
Andrews, 1990 [124]	1980–1989	56	18	Hospital
Dadoniene, 2005** [126]	1990–1999	48	36	Population-based
Ormerod, 2008 [128]	1995–2004	63	16	Hospital
Berti, 2017 [6]	1996–2015	67.7 (16.2)	28	Population-based
Mohammad, 2009 [130]	1997–2006	68.8	65	Population-based
Rathman, 2023 [133]	1997–2019	72*	159	Population-based
Reinhold-Keller, 2002 [134]	1998–1998	67	8	Population-based
Reinhold-Keller, 2002 [134]	1998–1998	57	4	Population-based
Reinhold-Keller, 2002 [134]	1999–1999	60	11	Population-based
Reinhold-Keller, 2002 [134]	1999–1999	65	3	Population-based
Nilsen, 2020 [135]	1999–2013	71	37	Population-based
Pierini, 2019 [136]	2000–2015	73.6 (13.2)	28	Hospital
Pamuk, 2016 [138]	2004–2014	61.5 (14.2)	15	Hospital
Pearce, 2016 [11]	2007–2013	70.2 (58.4–78.6)	107	Population-based
Bataille, 2022 [10]	2010–2017	67.0 (13.1)	878	Hospital

MPA, microscopic polyangiitis; SD, standard deviation

*Median age

**MPA and PAN considered together without distinction

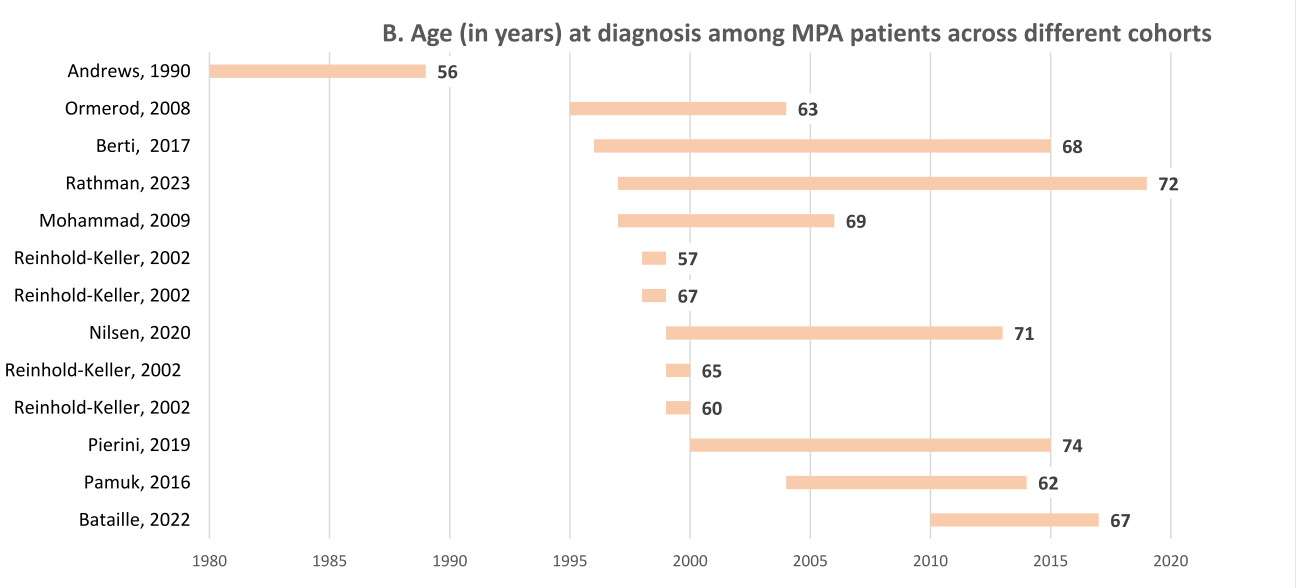

Fig. 2 Age at diagnosis across cohorts over time in MPA. Numbers represent the mean age (in years) at diagnosis of MPA in the different cohorts (references are indexed in Table 2), and the orange bars represent the follow-up duration of the cohorts. MPA, microscopic polyangiitis

an increase of memory T cells, especially cytotoxic CD8+ T cells in an advanced stage of differentiation [29]. Additionally, the expansion of a subset of cytotoxic CD8+ T named memory T cells with a I phenotype (TMNP) secreting proinflammatory factors such as TNFα, IFNγ, and granzyme B [30] has been reported as associated with aging.

T lymphocytes of older individuals have some intrinsic features that are consequences of telomere erosion, mitochondrial dysfunction, and oxidative stress. In fact, senescent T cells lose CD27 and CD28, as well as the expression of CD57, CD45RA, and/or KLRG-1 [31]. The downregulation of CD28 expression is due to chronic immune activation of human T lymphocytes, is a hallmark of replicative senescence, and correlates with impaired vaccine responses [32].

T cell senescence has been documented in several autoimmune diseases including systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, Sjögren's disease, and type 1 diabetes mellitus [33]. Only a few studies on T cell senescence in AAV have been published. During active disease in patients with AAV, it has been shown that there is a skewed distribution of Th17 and decreased T-regulatory cells [34], as well as expansion of a population of CD4+ T cells that lose CD28 expression and display potent effector function [35–37]. Whether these cells could resemble a "senescent" phenotype and contribute to tissue damage in AAV remains to be fully elucidated.

B cells undergo profound changes with aging, with a decrease in B cell differentiation in the bone marrow, redistribution of B cell subsets in the periphery—with an increase of proinflammatory B cells, decrease in expression of molecules required for class-switch recombination, somatic hypermutation, and germinal center formation, and decrease in repertoire diversity [27], which may reflect the reduced production of high-affinity protective antibodies [38, 39].

During aging, cellular skewing toward myeloid rather than lymphoid progenitors is observed, resulting from changes in the cytokines milieu within the bone marrow stem cell niches, including reduced production of IL-7 from bone marrow stromal cells [40] and dysregulation of epigenetic and transcriptional programs in hematopoietic stem cells [41].

The phenomenon of defective lymphopoiesis and B cell maturation is also reported in patients with AAV, in whom a reduced B-lymphoid precursor output from the bone marrow has been described. Furthermore, in contrast to other systemic autoimmune diseases [42], different studies have reported a decrease in the number of circulating transitional B cells in AAV [43, 44], which fail to replenish the peripheral B cell pool [44].

Aging can also affect the antibody production and the repertoire diversity. Studies have revealed that splenic B cells from old mice and mitogen-stimulated human B cells from older individuals are deficient in the production of class-switched isotypes as a consequence of the decreased expression of E47 and activation-induced cytidine deaminase [27, 45]. Changes in the antibody repertoire with aging, revealed by spectratyping of the Ig VH complementarity-determining region 3 (CDR3) of DNA samples from the peripheral blood, showed a significant collapse in repertoire diversity in the more elderly [46]. On the other hand, hyperexpansions of plasma cells, which can lead to

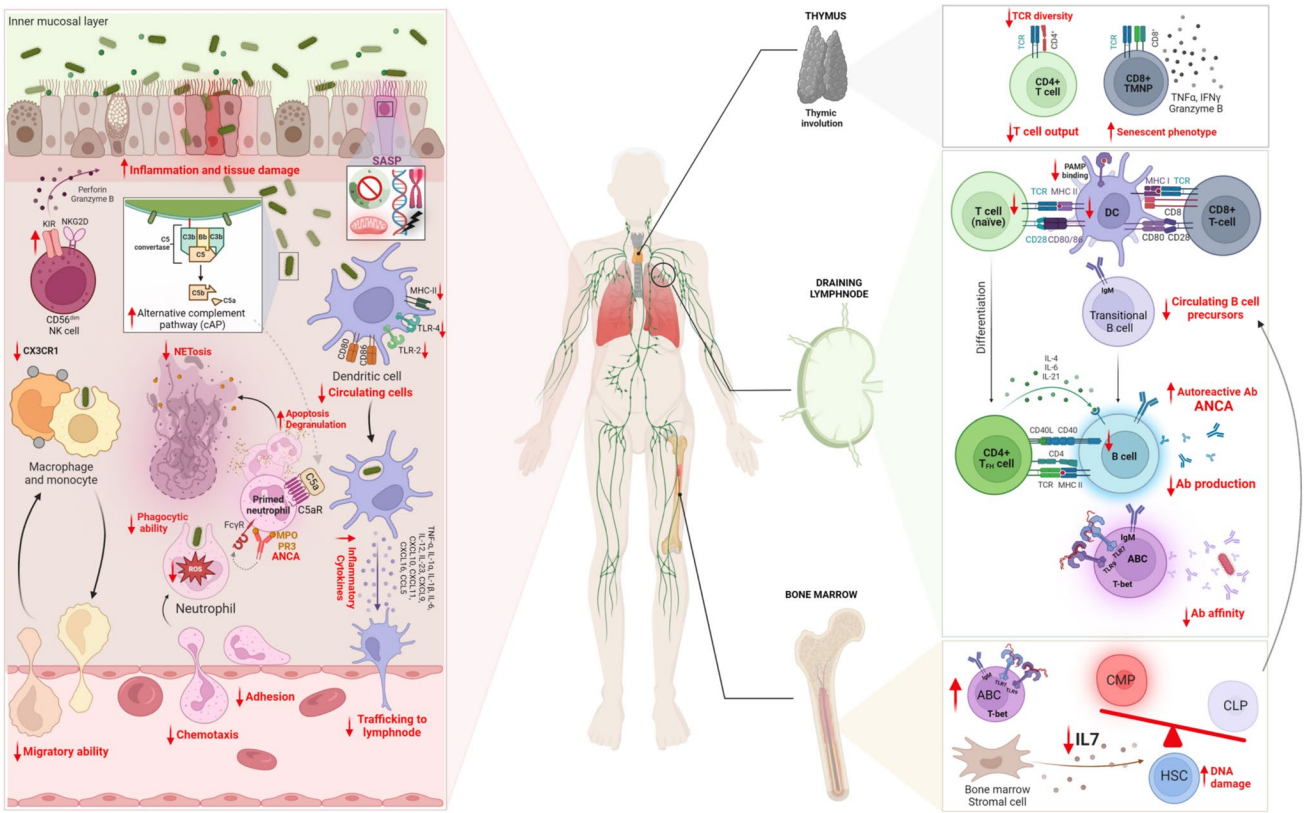

Fig. 3 Immunosenescence and aging may impact the development and progression of ANCA-associated vasculitis. Immune senescence is characterized by the alteration of various cellular subtypes and their interactions. In older subjects, the susceptibility toward autoimmunity is increased and dysregulations of the immune system due to aging may play a role in ANCA-associated vasculitis, where these cellular changes may lead to increased susceptibility to infections and an imbalance in the inflammatory response. Age-related B cells (ABC), anti-neutrophil cytoplasmic antibodies (ANCA), cluster of differentiation (CD), CX3C motif chemokine receptor 1 (CX3CR1), chemokine (C-X-C motif) ligand (CXCL), common lymphoid progenitor (CLP), common myeloid progenitor (CMP), human stem cells (HSC), interleukin (IL), killer-cell immunoglobulin-like receptor (KIR), major histocompatibility complex class II (MHC-II), natural killer group 2 member D (NKG2D), reactive oxygen species (ROS), senescence-associated secretory phenotype (SASP), T cell receptor (TCR), Toll-like receptor (TLR), memory T cells with a naive phenotype (TMNP), tumor necrosis factor (TNF)

monoclonal gammopathies of undetermined significance and other monoclonal B cell expansions, are also associated with aging [47].

Even though a decrease of a repertoire diversity has not been shown in AAV, an oligoclonal expansion of autoreactive B cells during active disease is plausible, and this hypothesis is supported by the expansion of autoreactive memory B cells and autoreactive plasmablasts in patients with AAV [43, 48].

Finally, studies in older mice have revealed an increase in age-associated B cells (ABCs) in the bone marrow. These are defined as a transcriptionally and functionally unique B cell population expressing T-bet, CD11c, CD11b, and lack of CD21, being shown to increase during aging, infections, and autoimmunity [49, 50]. They represent a proinflammatory subset that secretes high levels of TNFα and hinders pro-B cell generation [51]. ABCs are unresponsive to B-cell receptor (BCR) and CD40 stimulation but are activated by TLR7/9 stimulation, resulting in more innate-like immune responses and the production of low-affinity antibodies [49, 50]. ABCs also play a role in autoantibody production, potentially contributing to autoimmunity in the older [50]. In this context, it has been shown that stimulation of TLR-9 via CpG oligodeoxynucleotide (CpG-ODN) can enhance ANCA production by B cells from patients with AAV [52].

4 Diagnosis, Assessment, and Comprehensive Care in the Elderly

The diagnosis and evaluation of the severity of ANCA-associated vasculitis necessitates a comprehensive array of clinical, imaging, and biological tests [53].

Few studies have explored the clinical features of older compared with younger patients (Fig. 4, Table 3). The two groups differ in some clinical or biological characteristics. [54, 55]

In particular, the incidence of ANCA-associated vasculitides (AAV) is higher in older patients, whose clinical presentation is often different with respect to younger patients, with lower frequencies of ear, nose, and throat (ENT) involvement and higher frequencies of respiratory manifestations (Fig. 4, Table 3).

4.1 Frailty Assessment to Characterize the Physiological Reserve of Older Patients

Currently, most studies rely on age as a criterion to stratify younger and older patients. However, the cutoff values are arbitrary and might not reflect patients' physiological aging. Although 65 or 75 years are often selected as thresholds to define older patients, the concept of frailty offers more insight into the physiological capacity to endure stressful diseases and treatments such as AAV and its management.

Frailty is a state of diminished physiological reserve, reflective of biological age. The interplay between two complementary concepts contributes to the definition of frailty [56]. They highlight the deep impact of frailty on patients' quality of life, morbidity, and life expectancy [57]. On the one hand, there is frailty as the accumulation of health deficits [58], and on the other hand, there is the overall vision of frailty as a syndrome [59] characterized by exhaustion (the first symptom), weakness, slowness, physical inactivity with loss of energy, and weight loss. Frailty assessment is associated with health outcomes. It ranges from categories such as "fit" and "prefrailty" to "frailty" and "end-stage frailty," assessed using tools such as the deficit-accumulation frailty index or the frailty score [56]. It is directly associated with comorbidities and multimorbidity, and a bidirectional link between those two can be suggested [60, 61].

Since frailty makes older people more vulnerable to the risks associated with care, the frailty assessment is crucial for decision-making about invasive diagnostic procedures such as biopsies or stressful treatments such glucocorticoids and immunosuppressants. In 2020, a Scottish study included 83 patients with AAV older than 65 years to evaluate frailty as a prognostic factor [62]. Frailty was gradually associated to death, doubling the risk of death for each point on the Rockwood Clinical Frailty Scale (RCFS, hazard ratio 1.90 per point). Furthermore, the frailer group (RCFS $\geq$ 4, "vulnerable" patients) experienced a longer duration of hospitalization and higher mortality. The 5-year mortality was 90% in the frailer group, versus 47% in the "managing well" patients (RCFS $\leq$ 3). Another study included 32 patients with AAV and evaluated the risk of death according to the Hospital Frailty Risk Score (HFRS). Although no difference in mortality was found across the HFRS groups, length of stay was much longer in the high HFRS group compared with the low and medium HFRS groups (29 days versus 4 and 7 days, respectively) without reaching the significance threshold. [63]

4.2 Clinical and Biological Differences across Age Groups

In general, older AAV patients are more likely to present nonspecific symptoms [64], leading to diagnostic delays and exacerbating renal injuries in patients over 60 years old versus under 60 years old [65]. Similarly, older patients are more likely to display elevated inflammatory markers (C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)) [66]. Pulmonary infiltration, interstitial fibrosis, and mechanical ventilation dependence at presentation were more common in patients over 65 years old as compared with those under 65 years. In addition, among two Chinese AAV cohorts, more pulmonary fibrosis and alveolar infiltration was found in older patients, while no difference was found regarding nodules [66, 67]. Data regarding age-related differences in the estimated glomerular filtration rate (eGFR) are contradictory [66–70] and could be influenced by the natural aging of the renal function. AAV represent 19% of all kidney biopsies in patients aged 80 years and above [71]. Renal function decline is more severe in older patients and worsens with age. However, in a single Chinese cohort, it was shown that patients with AAV aged over 65 years demonstrated a lower urinary protein level compared with the others (1.67 g/24 h versus 2.45 g/24 h) [66]. Interestingly, in renal biopsies performed at AAV diagnosis and before any immunosuppressive treatment, no significant differences arose in the histologic lesions across age groups [55, 66, 67].

Patients $\geq$ 60 years old present significantly less ENT involvement than younger individuals [54, 65, 66, 69]. As well, several papers have reported that central nervous system (CNS) involvement occurred 4–5-fold more in patients older than 60 years [65, 68] with concomitant peripheral neuropathy [65]. Older patients with AAV were more likely to present peripheral nervous system involvement, mainly as mononeuritis multiplex [65].

The proportion of females decreases with age at diagnosis (62% in young adults versus 51% of middle-aged adults and 52% of older adults), while myeloperoxidase (MPO)-ANCA positivity increases with age [68]. Overall, MPO-ANCA detection was higher as compared with proteinase 3 (PR3)-ANCA among patients older than 65 years old, and the diagnosis of MPA was more frequent in these age group as compared with GPA [66]. The intersection between age and clinical diagnosis/ANCA subset affects the presentation of GPA/MPA in different age groups. In addition to the effect of AAV on patients, aging contributes to the decline in organ function.

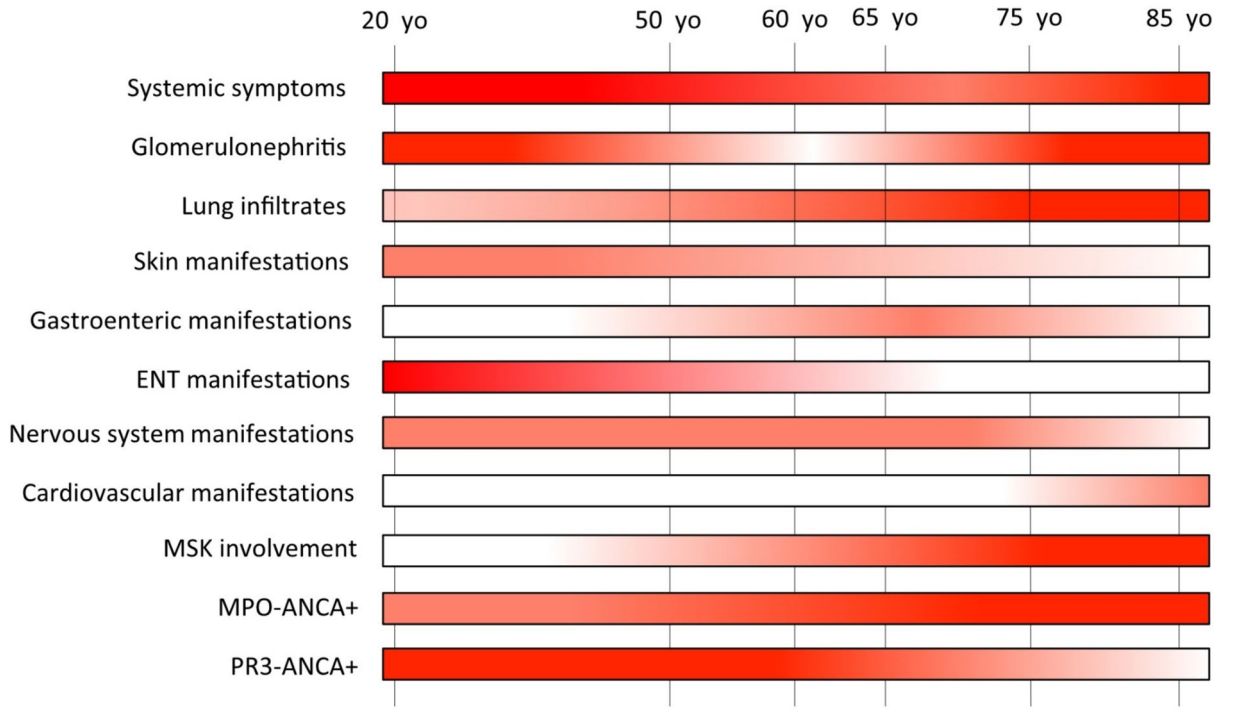

Fig. 4 Frequencies of ANCA-associated vasculitis clinical manifestations across age spectrum. This figure illustrates the distribution of clinical manifestations of ANCA-associated vasculitis across different adult age groups. Each bar visually represents the reported frequencies of a specific symptom or organ involvement at various ages, based on data from multiple studies (see Table 3 for percentages). Higher frequencies are indicated by more intense red. Data collected from Refs. [54, 65–68, 70, 123, 140] and are also presented in Table 3. In Bjørneklett et al. [123], patients ≥ 75 years old were compared with 70–74-year-old patients. In Meng et al. [67], patients were classified as < 65, 65–74, ≥ 75 years old. ANCA, antineutrophil cytoplasmic antibodies; ENT, ear, nose, throat; MPO, myeloperoxidase; MSK, musculoskeletal; PR3, proteinase 3; yo, years old

5 Treatment of GPA and MPA in Older Patients

As of today, the management of AAV falls within the expertise of rheumatologists, pulmonologists, nephrologists, or specialized clinicians of organ systems involved in AAV. However, geriatricians should ideally also be included in decision-making, given the significant amount of high-quality evidence related to the management of patients characterized by frailty [72–74]. In older patients, frailty should guide treatment decisions, particularly in assessing the balance between immunosuppressant efficacy and drug safety.

Treatment of GPA and MPA depends on the severity of the disease. European Alliance of Associations for Rheumatology (EULAR) recommendations and American College of Rheumatology (ACR) guidelines refers to "organ/life threatening disease" or "severe disease," for which different regimens of immunosuppression may be considered [75]. Immunosuppressive treatment is imperative, divided into two sequential phases.

The remission induction phase is designed to achieve remission, mainly defined as no disease activity, possibly assessed using a disease activity score such as the Birmingham Vasculitis Activity Score [76] (BVAS). Usually, the remission induction treatment consists in the use of high-dose glucocorticoids with either cyclophosphamide or rituximab.

The maintenance regimen aims to sustain remission, i.e., prevent relapses and avert disease-related treatment complications while decreasing the intensity of immunosuppression. In general, a low maintenance dose of glucocorticoids, disease-modifying antirheumatic drugs (DMARDs), or the scheduled or individually timed use of rituximab are considered for maintenance of remission.

Some patients present with non-life/organ-threatening disease or "nonsevere" disease. For induction of remission in such patients, rituximab is also increasingly used in addition

Table 3 Characteristic manifestations of "older patients" in ANCA-associated vasculitis and changes in clinical presentations

Manifestation	≥ 60 years old [65]	≥ 65 years old [66–68, 70, 121, 140]	≥ 75 years old [54, 67, 123]
Systemic symptoms (fever, fatigue, weight loss)		45–84%	68–84%
Glomerulonephritis	18%	74–94%	65–88%
Lung infiltrates	27%	61–90%	76%
Skin manifestations		3–37%	8–11%
Gastrointestinal manifestations		0–30%	4–7%
ENT manifestations	12%	10–53%	24–73%
Eye involvement		14–22%	21%
Nervous system manifestations		21–33%	16–18%
Cardiovascular manifestations		2–19%	24%
MSK involvement		35–73%	
MPO-ANCA+		61–95%	57–84%
PR3-ANCA+		5–27%	16%
Anemia		88–89%	

The table summarizes key clinical features of ANCA-associated vasculitis in older patients by age group. Percentages are frequencies reported in the studies referenced in the table

In Bjørneklett et al. [123], patients ≥75 years old were compared with 70–74-year-old patients. In Meng et al. [67], patients were classified as < 65, 65–74, ≥ 75 years old

ANCA, antineutrophil cytoplasmic antibodies; ENT, ear, nose, and throat; MPO, myeloperoxidase; MSK, musculoskeletal; PR3, proteinase 3

to glucocorticoids, presumably because of greater efficacy in relapsing and PR3-ANCA-positive AAV, which account for the majority of patients with nonsevere disease presentations or relapses [2, 77, 78] However, methotrexate and mycophenolate mofetil remain valid alternatives.

5.1 Remission Induction Phase

5.1.1 Glucocorticoids

The induction of severe or organ-threatening AAV is mainly based on glucocorticoid pulses (IV methylprednisolone 500–1000 mg/day during 3 days [75, 79]) followed by 1 mg/kg oral prednisone-equivalent. After pulses, glucocorticoids must be continued for remission, and gradually tapered. Glucocorticoids present numerous short-term and long-term adverse effects [80], and those are more prevalent in older than younger patients [70, 81].

Trials have aimed to minimize glucocorticoid exposure while achieving remission. Recently, two studies showed that lower glucocorticoid doses may be sufficient to induce remission, with less adverse effects, i.e., the PEXIVAS study and LOVAS study (the latter excluding patients with severe glomerulonephritis and alveolar hemorrhage). The reduced glucocorticoid dosing scheme from the PEXIVAS trial has been adopted by most of the available guidelines [75, 79]. No age-based analysis was performed in either of the trials.

The single randomized, open-label trial focusing on older patients suffering from AAV, CORTAGE [64], included patients older than 65 years with AAV or polyarteritis nodosa. As immunosuppressive treatments affect more frail populations such as the older [81, 82], one of the main objectives of this study was to determine the optimal doses of glucocorticoids and cyclophosphamide. The aim of the study was to identify the immunosuppressant dose that effectively controls the disease while limiting the immunosuppressant-induced side effects in older patients with AAV. One hundred four patients were included, with 36 having GPA and 44 having MPA. Mean ± standard deviation (SD) age was 75.2 ± 6.3 years at diagnosis, and vasculitis involvements and comorbidities were similarly distributed over both treatment groups. The experimental group received glucocorticoids for 9 months, and from three to a maximum of six pulses of fixed 500-mg doses of cyclophosphamide to enter remission, followed by maintenance with azathioprine or methotrexate. The control group received the "usual standard" regimen with glucocorticoids for 26 months and 500 mg/m^2 pulses of cyclophosphamide until remission. The mean cyclophosphamide dose received in the control arm was 5586 mg, and the experimental arm received significantly less cyclophosphamide (2688 mg, $p < 0.01$), which corresponds to a mean ± SD exposure of 7.4 ± 2.6 versus 5.3 ± 1.2 pulses, respectively. In both groups, azathioprine or methotrexate was used for remission maintenance after completion of cyclophosphamide therapy for a total of 18 months. The

global survival did not differ between the groups. The remission rate was not different between the two treatment groups, but severe adverse events were significantly lower in the group receiving lower doses of glucocorticoids and cyclophosphamide (22% versus 40% after 36 months of follow-up, $p = 0.04$).

Another study nested in two nationwide prospective Japanese cohorts [83] included 179 patients aged ≥ 75 years suffering from GPA, MPA, or EGPA. The patients were divided into three groups on the basis of glucocorticoid dosage: high dosage (≥ 0.8 mg/kg/day), medium dosage (0.6 ≤ glucocorticoids < 0.8 mg/kg/day) and low-dosage (< 0.6 mg/kg/day). No difference in remission or relapse rate was found between the groups. The main limit of this retrospective study is likely the selection of glucocorticoid dose in patients according to their disease severity, which can also influence relapse risk. Notably, more infections occurred in the group who received the highest glucocorticoid level, compared with the other two groups. Therefore, despite its retrospective design, this study suggests that a lower dose of glucocorticoids in older patients might achieve AAV remission while reducing adverse events.

5.1.2 Immunosuppressive Treatments: Cyclophosphamide and Rituximab

A meta-analysis based on three different studies evaluated the impact of induction treatment on the risk of death or end-stage renal disease (ESRD) [84]. These studies included a total of 290 AAV patients older than 75 years. Among this population, the group receiving treatment to induce remission was associated with a 71% reduction in the risk of death compared with patients not receiving remission induction therapy; this was irrespective of the drug chosen for treatment (cyclophosphamide or rituximab). Nonetheless, the risk of ESRD after 2 years was not different. Similar results were found in a subanalysis focusing on patients aged ≥ 80 years. This study suggests beneficial outcomes and safety of inducing remission with immunosuppressive treatments in older patients.

While cyclophosphamide induces remission in AAV, its use is constrained by potential oncologic and infectious adverse events. In a retrospective multicentric cohort mainly treated for remission induction with cyclophosphamide, the susceptibility to disease- and treatment-related morbidity was significantly higher in older than in younger patients, particularly the loss of renal function and infection rate [70]. In a recent retrospective study including 197 patients with MPA and GPA, younger AAV patients received a combination of cyclophosphamide and rituximab more often than older patients (37% of young adults, 27% of middle-aged adults, and 14% of adults ≥ 65 years) [68]. The retrospective design of the study hinders the interpretation of the prescription, and combination of rituximab and cyclophosphamide might have been prescribed either in more severe disease or in less frail patients. After 4.3 years on average, damage was similar in older patients compared with middle-aged or young patients.

The efficacy and safety of a low-dose scheme of cyclophosphamide were assessed in a retrospective study [69]; 41 patients ≥ 65 years old were included and compared with 52 patients younger than 65 years. BVAS at diagnosis was similar in the age groups, but the urinary protein excretion was lower in the older (1065 versus 1947 mg/24 h, $p = 0.04$). Comorbidities were more frequent in the older group. Cyclophosphamide dose at induction was significantly lower in the older patients (2400 mg versus 4800 mg, $p = 0.007$; 8.9 mg/kg body weight versus 10 mg/kg body weight, $p = 0.037$). As well, the intravenous methylprednisolone dose was lower among the older than among the younger patients (2250 mg versus 3000 mg/kg, respectively, $p = 0.004$). Then, oral prednisone was gradually decreased within both groups from 1 mg/kg/day to 4 mg/day in 6 months. Deaths due to cardiovascular events were more frequent in the older group, whereas deaths due to disease activity or infection were similar. Death in the short term occurred nearly twice more frequently in the older group, and half the deaths arose in the 4 months after the start of induction treatment.

Rituximab is effective to induce remission in AAV [2, 85]. Rituximab is the preferred choice for relapsing disease according to EULAR recommendations, and for both new-onset and relapsing AAV according to ACR guidelines [75, 79]. Similarly, rituximab is preferred for new-onset and relapsing AAV in the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, in particular for the older patients [86].

In a retrospective study including old AAV patients who received rituximab at remission induction, Thietard et al. [87] reported a 86.4% remission rate among 66 patients aged ≥ 75 years. Six patients (9.1%) died before achieving remission [87]. Similar results were found in another smaller retrospective cohort involving AAV patients aged ≥ 60 years undergoing rituximab induction for remission (remission in 30/31) [88]. These remission rates among older patients surpass the remission rates found in two previous randomized controlled trials assessing rituximab versus cyclophosphamide and including younger patients, although this apparent difference may relate to the different remission definitions between prospective and retrospective studies [2, 85]. Bomback et al. [89] conducted a retrospective study including patients older than 80 years old at diagnosis and assessed efficacy and adverse events of the immunosuppressive treatments (i.e., cyclophosphamide, azathioprine, glucocorticoids, and plasma exchange). The immunosuppressed group included 50 AAV patients, while the control group without any immunosuppressive treatment included

11 subjects. The risk of developing ESRD within the first year was significantly lower in the immunosuppressed group (36% versus 73% in the control group; $p = 0.03$), but interestingly the 1-year mortality did not differ between the two groups (47% among immunosuppressed patients versus 64% in the control group; $p = 0.3$), hypothesized to be caused by the morbidity induced by conventional immunosuppressants. Then, the mortality rate at 2 years was significantly lower in the immunosuppressed group, as well as the rate of ESRD. Thietard et al. [87] also showed that infections were more frequent during the induction than the maintenance phase (46.6 serious infections per 100 patient-years versus 8.4 per 100 patient-years, respectively, $p = 0.004$). Likewise, in a previous randomized controlled trial [77] assessing efficacy of rituximab versus azathioprine in relapsing AAV, infections in patients receiving rituximab occurred early after infusion.

In conclusion, rituximab is effective and may be considered as the first-line therapy (1000 mg IV twice, 2 weeks apart, or 375 mg/m^2 weekly for 4 weeks) for remission induction of GPA and MPA, and could be considered as a preferred therapy in older patients with AAV.

5.1.3 Avacopan

In the ADVOCATE study, the first-in-class drug avacopan (a synthetic C5aR inhibitor) showed efficacy in the remission induction treatment of AAV [4]. Three hundred thirty patients were randomized into two groups: in addition to rituximab or cyclophosphamide associated with methylprednisolone pulses for induction remission, the protocol prescribed either prednisone for a maximum of 4 weeks and avacopan for 1 year, or a standard prednisone tapering regimen (and a placebo of avacopan). The mean age of the patients was 60 years, and avacopan was found to be noninferior in achieving remission at 6 months and superior to the glucocorticoid arm for sustaining remission to 12 months. A post hoc analysis of the ADVOCATE study reported similar safety and efficacy of avacopan in the 160 patients aged ≥ 65 years at enrolment, compared with the overall cohort [90].

A Japanese team [91] analyzed the subgroup of the 21 Japanese trial participants, and compared them with the whole cohort. Japanese patients were slightly older than the other patients of the cohort (mean age 75.5 years in the avacopan group versus 69.6 years in the control group). Among these older patients, more patients receiving avacopan achieved remission by month 6 compared with the glucocorticoid control group (81.8% versus 70.0%) and more individuals sustained remission through week 52 (72.7% versus 40.0%). The results of this small group of Japanese ADVOCATE trial participants suggests that avacopan is at least as effective as glucocorticoids in older patients.

5.2 Remission Maintenance Phase

Rituximab has been shown to be more effective than azathioprine for maintaining remission without causing more severe adverse events, and several rituximab retreatment schemes have been evaluated [92].

In the MAINRITSAN 3 study [93], the duration of rituximab required for maintaining long-term remission was investigated. Patients receiving rituximab for 3 years experienced no major relapse, while 13% of patients receiving placebo after an 18-month rituximab treatment course had a major relapse ($p = 0.009$). The mean age was 64 years, and adverse events increased with the rituximab dose [94]. The safety of long-term rituximab in AAV is reassuring [95, 96], but no study has specifically evaluated long-term rituximab in older patients with AAV.

6 How to Manage Treatment Side Effects and Complications

6.1 Infectious Comorbidities

Immunosuppressants can reduce the response against both environmental microbial agents as well as internal colonizing microbial agents, potentially leading to active infections that were previously controlled. Moreover, immunosuppression can mute the response to vaccinations.

In a large retrospective study collecting data of 234 AAV patients, outcomes, deaths, and ESRD were compared in patients aged 65–74 years versus those older than 75 years [72]. Outcomes were assessed across different frailty stages. Patients were classified as non-frail, pre-frail, mildly frail, or moderately and severely frail according to the claims-based frailty index (CFI) [97]. The CFI collects information in the year before the index date across 93 variables to estimate biological age. MPO-ANCA was found in 85% out of the 234 patients. Over a follow-up of 2 years, infections were significantly more numerous among patients aged 75 years or older than in patients aged 65–74 years (hazard ratio [HR] 4.60), but not among more frail patients. Regarding severe infections, the risk was higher in both more frail patients (HR 8.49) and among patients aged ≥ 75 years (HR 3.22). The different findings regarding age and frailty highlight the importance of frailty assessment in the care of older people.

Pneumocystis pneumonia prophylaxis [98, 99] should be given to all AAV patients with oral trimethoprim–sulfamethoxazole, atovaquone, or aerosolized pentamidine in cases of trimethoprim–sulfamethoxazole intolerance or allergy. Despite lack of evidence about how long to continue prophylaxis, it is common practice to continue

prophylaxis for as long as B cells remain depleted in patients who received rituximab, and for as long as lymphopenia persists in patients treated with cyclophosphamide and azathioprine [100]. These authors [100] also advocate for pneumocystis pneumonia prophylaxis for patients treated with methotrexate or mycophenolate mofetil, particularly when used in combination with glucocorticoids, and in older patients, whose immune system is already weakened from senescence at baseline. To date, no study has specifically addressed the risk of pneumocystis pneumonia in AAV patients treated with methotrexate or mycophenolate mofetil.

Pneumococcal, influenza, respiratory syncytial virus (RSV), and shingles vaccination should be considered in all patients with AAV, and this is particularly true for older patients (for whom these vaccinations are recommended in most countries on the basis of age of 65 years or older alone, regardless of underlying condition or immunosuppressive treatment [98]). Hepatitis A (HAV) or hepatitis B (HBV) vaccinations should be administered to AAV patients traveling or resident, respectively, in HAV- or HBV-endemic countries. HBV vaccination should also be administered to patients at increased risk of exposure to HBV. Finally, EULAR recommends coronavirus disease 2019 (COVID-19) vaccinations for all patients with rheumatic disease, including AAV [101].

Vaccinations are generally considered ineffective when given at times of B cell depletion after rituximab treatment. While the antibody response is absent during B cell response, antigen-specific T cell responses seem to be normal, but it is unknown whether this conveys any protective effect [102, 103]. This adverse effect of rituximab can be mitigated if retreatment for remission maintenance is timed individually on the basis of B-cell reconstitution rather than scheduled every 6 months [93, 104].

6.2 Treatment-Associated Risk of Cancer

Age is a major risk factor for numerous neoplasms. Hence, older patients receiving immunosuppressive treatments should undergo careful cancer screening.

Cyclophosphamide increases the risk of malignancy threefold in AAV patients compared with the general population [105], and particularly the risk for renal and bladder cancers [106]. This urothelial cancer risk can be mitigated with the use of uromitexan if cyclophosphamide is given intravenously. Patients who receive oral cyclophosphamide should be advised to take the drug as a single dose in the morning and ensure generous fluid intake for the rest of the day. Conversely, rituximab has not been found to increase the malignancy risk in AAV patients [105], or among patients suffering from other rheumatic diseases. Finally, the risk for non-melanoma skin cancers associated with long-term use of azathioprine is noteworthy here, particularly in older patients who have accumulated substantially more sun damage than younger patients.

6.3 Osteoporosis and Glucocorticoid Side Effects

As the most significant decrease of bone mineral density (BMD) occurs in the first 3–6 months after glucocorticoid pulses and high doses [107], glucocorticoid-induced osteoporosis should be addressed promptly. Recent recommendations published by the American College of Rheumatology (ACR) recommend osteoporosis prophylaxis for any patients receiving more than a 3-month course of glucocorticoids. Oral or IV bisphosphonates, denosumab, and parathyroid hormone(PTH)/PTHrp analogs are recommended in first-line therapy for osteoporosis [107]. The fracture risk should be assessed as soon as possible after starting glucocorticoids, and reassessment should be performed yearly. Supplemental calcium has to be considered for an optimal daily intake of 1000–1200 mg/day, as well as vitamin D (600–800 IU/day) to maintain serum vitamin D level > 30–50 ng/mL [107].

Moreover, several other glucocorticoid side effects including arterial hypertension, diabetes mellitus, cataracts, cerebrovascular accidents, myocardial infarctions, and others [108] are also correlated with age, and should therefore be specifically sought and prevented.

6.4 Hypogammaglobulinemia Induced by B-Cell Targeted Therapies

Hypogammaglobulinemia after B-cell targeted therapies such as rituximab is common and increases the risk of infections [109]. Age impacts gammaglobulin concentrations regardless of the treatment [110]. Furthermore, hypogammaglobulinemia induced by B-cell targeted treatment is more frequent in AAV patients than in patients with other connective tissue diseases [111]. In AAV, the risk for hypogammaglobulinemia is particularly high in patients who also received cyclophosphamide [112]. Among a large cohort of patients suffering from various rheumatologic diseases, rituximab was shown to slightly increase the mortality when associated with age (hazard ratio 1.03, 95% confidence interval 1.02–1.04) [113]. Therefore, immunoglobulin levels should be monitored every 6–12 months [114], and immunoglobulin replacement therapy decisions should be guided by individual patients' infection history [114]**.** Primary prevention with antibiotic prophylaxis is not recommended for hypogammaglobulinemia [114].

7 Follow-Up and Prognosis

7.1 Hospitalization Rates and Outcomes

In multiple studies following patients for all causes [59, 115–118], frail patients were 30–60% more likely to be hospitalized compared with robust people of the same age, and this risk was also 1.2 times higher when compared with prefrail patients [59, 115–118].

Among all hospitalized patients admitted for any unplanned reason, frail patients had a 2.5-fold risk of death [119]. Moreover, increasing severity of frailty was associated with an increased risk of death up to 1 year after hospital admission.

The length of hospitalization also doubled in frail older patients, both in the general population [119] and among AAV patients [62, 63].

7.2 Damage

Damage in vasculitis can be measured by several index scores, including the Vasculitis Damage Index (VDI) score [120]. A recent study found that patients diagnosed with GPA or MPA at more advanced age have a higher amount of damage than those diagnosed at younger ages, but these differences are driven by non-disease-specific damage, such as medication toxicity or comorbidities [68].

Another study showed that patients older than 65 years are two-fold more likely to develop a VDI score ≥ 5 than younger patients [121].

7.3 Relapse, End-Stage Renal Disease, and Death Risks

In a population-based study, the overall standardized mortality ratio (SMR) was determined to be twice as high in patients with AAV as in the general population [6]. Death from all causes was higher among older in comparison with younger patients [54, 55, 67]. This distinction becomes irrelevant when looking specifically at patients with renal AAV [67].

A retrospective study of 300 AAV patients revealed that the relapse-free survival was higher in individuals aged 75 years and above compared with those aged 65–75 years [72, 87, 122]. The relapse assessment included all-cause mortality. The 48-month relapse-free survival was 76% for patients aged 75 years and above and 52% ($p < 0.001$) for those aged 65–75 years. Patients aged ≥ 75 years were significantly more likely to receive rituximab, while those aged 56–75 years received more cyclophosphamide. This study presents important findings and suggests a reduction of relapse rate in older patients. This underscores the importance of age stratification in evaluating relapse outcomes in patients with AAV, shedding light on potential variations in disease trajectories based on age groups.

Assessment beyond chronological age such as frailty might be needed and could inform the risk assessment. Frailty at AAV diagnosis was gradually associated with an increased risk of death [62], although these results are controversial, and no association with mortality was found in two cohorts [63, 72]. In particular, a large study including 234 AAV patients [72] aged 65 years or older showed differences in the cumulative risk of ESRD or death between age and frailty classification of patients. Over the 2 years following the diagnosis, multivariable analysis found that patients aged 75 years and older had a 4.50-fold higher risk (95% CI 1.83–11.09) compared with those younger than 75 years at AAV diagnosis. In contrast, there was no significant difference in the risk of death or ESRD in the frail patients compared with both non-frail and pre-frail patients.

Among older patients, histological types in renal biopsies are not a predictor of risk of death [123]. However, histological types in renal biopsies are predictive of ESRD, with a higher risk among patients displaying a sclerotic aspect in glomerules [123].

8 Conclusions

The incidence of AAV in older patients seems to be growing, along with the global aging of general populations. Of note, data on immunoaging for AAV are scant.

Even though most AAV manifestations are similar among different age groups, older patients present more often anti-MPO-ANCA, and some characteristics may be more common, such as renal manifestations or the association with interstitial lung disease.

Current guidelines recommend selecting treatment regardless of the age of adult patients with AAV. However, accumulating findings are supporting the preferred use of rituximab as a first-line agent in older patients for induction and maintenance of remission. Rituximab was shown to be safe at remission induction in older patients and reduced ESRD and death risk, while data concerning remission maintenance are reassuring. Preliminary data in older individuals showed safety and efficacy of avacopan, and this new treatment option may be particularly attractive for older patients because of its potential to minimize glucocorticoid use and better preserve renal function. Comorbidities and damage are increased in older compared with younger patients. Therefore, prophylaxis and early treatment of infections as well as effective prevention of relapses and treatment-related damage are crucial in this population.

Since frailty plays a pivotal role in treatment decision-making, geriatricians should be included in the care of patients

with AAV. Also, more geriatrician-driven studies are needed to focus on those patients in whom inflammaging may lead to differences in management.

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