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Leczenie i jego powikłania u pacjentów z zapaleniami naczyń związanymi z przeciwciałami przeciw cytoplazmie neutrofilów (ANCA) - retrospektywna analiza na podstawie wieloośrodkowego rejestru chorych.

Treatment and its side effects in patients with ANCA- associated vasculitides – retrospective analysis, based on the multicentre data registry.

Praca doktorska – cykl prac monotematycznych.

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SPIS TREŚCI

I. PUBLIKACJE WCHODZĄCE W SKŁAD PRACY DOKTORSKIEJ

1. Grzegorz Biedroń, Anna Władarczyk, Katarzyna Wawrzycka-Adamczyk, Krzysztof Wójcik, Jan Sznajd, Zbigniew Zdrojewski, Anna Masiak, Zenobia Czuszyńska, Maria Majdan, Radosław Jeleniewicz, Marian Klinger, Katarzyna Jakuszko, Olumide Olatubosun Rowaiye, Marek Brzosko, Iwona Brzosko, Alicja Dębska-Ślizień, Hanna Storoniak, Witold Tłustochowicz, Joanna Kur-Zalewska, Małgorzata Wisłowska, Marta Madej, Anna Hawrot-Kawecka, Piotr Gluszko, Eugeniusz J. Kucharz, Jacek Musiał, Wojciech Szczeklik.
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2. Grzegorz Biedroń, Anna Władarczyk, Katarzyna Wawrzycka-Adamczyk, Krzysztof Wójcik, Jacek Musiał, Stanisława Bazan-Socha, Zbigniew Zdrojewski, Anna Masiak, Zenobia Czuszyńska, Maria Majdan, Radosław Jeleniewicz, Marian Klinger , Magdalena Krajewska, Hanna Augustyniak-Bartosik, Katarzyna Jakuszko, Marek Brzosko, Iwona Brzosko, Alicja Dębska-Ślizień, Hanna Storoniak, Barbara Bułło-Piontecka, Witold Tłustochowicz, Joanna Kur-Zalewska, Małgorzata Wisłowska, Marta Madej, Anna Hawrot-Kawecka, Piotr Gluszko, Eugeniusz J. Kucharz, Wojciech Szczeklik.
   Respiratory involvement in ANCA-associated vasculitides - a retrospective study based on POLVAS registry.
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3. Anna Władarczyk, Grzegorz Biedroń, Krzysztof Wójcik, Zbigniew Zdrojewski, Anna Masiak, Zenobia Czuszyńska, Maria Majdan, Radosław Jeleniewicz, Magdalena Krajewska, Mariusz Kusztal, Marek Brzosko, Iwona Brzosko, Alicja Dębska-Ślizień, Hanna Storoniak, Witold Tłustochowicz, Joanna Kur-Zalewska, Andrzej Rydzewski, Marta Madej, Anna Hawrot-Kawecka, Małgorzata Stasiek, Eugeniusz J. Kucharz, Jacek Musiał, Wojciech Szczeklik.
   ANCA-associated vasculitis patients treated in polish intensive care units – retrospective characteristics based on POLVAS registry.

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II. WSTĘP TEORETYCZNY I PODSTAWY PRACY

Układowe zapalenia naczyń, związane z przeciwciałami przeciw cytoplazmie neutrofilów – ANCA (ang. ANCA-associated vasculitides; AAV) to grupa rzadkich chorób o niewyjaśnionej etiologii. Zgodnie z konsensusem z Chapel Hill z 2012 r. w grupie AAV wyróżnia się 3 odrębne jednostki kliniczne – ziarniniakowatość z zapaleniem naczyń (ang. granulomatosis with polyangiitis; GPA), mikroskopowe zapalenie naczyń (ang. microscopic polyangiitis; MPA) oraz eozynofilową ziarniniakowatość z zapaleniem naczyń (ang. eosinophilic granulomatosis with polyangiitis; EGPA) [1]. Roczną zapadalność szacuje się na 1,2-3,3/ 100 000 przypadków dla całej grupy AVV [2], a dla poszczególnych jednostek w populacjach europejskich na 4,9-10,2/ milion przypadków dla GPA, 2,7-11,6/ milion dla MPA i 0,5-4,2/milion dla EGPA [3]. Patomechanizm rozwoju tych schorzeń ma podłoże autoimmunizacyjne, w którym kluczową rolę odgrywają nieprawidłowości w funkcjonowaniu układu immunologicznego m.in. neutrofilów (patologiczna, nadmierna aktywacja, uwalnianie zewnątrzkomórkowych pułapek neutrofilowych [ang. NETs – neutrophil extracellular traps]), układu dopełniacza (pobudzenie alternatywnej drogi aktywacji układu dopełniacza, chemotaksja i aktywacja neutrofilów poprzez składową C5a układu dopełniacza), limfocytów (produkcja patologicznych przeciwciał ANCA przez limfocyty B przy współudziale limfocytów Th, zaburzenia funkcji regulatorowych limfocytów Treg, produkcja cytokin prozapalnych przez limfocyty Th17), makrofagów (udział w nadmiernej aktywacji neutrofilów) [4-7]. W przypadku EGPA, która wykazuje znaczną odrębność w porównaniu z pozostałymi AAV, istotny wkład w patogenezę ma nieprawidłowa aktywacja eozynofilów [8]. AAV powodują zapalenie głównie drobnych naczyń, których uszkodzenie prowadzi do zmian narządowych, zależnych od dystrybucji zapalenia. W przebiegu tej grupy chorób może dojść do zajęcia niemal każdego narządu, choć poszczególne jednostki kliniczne wykazują predylekcję do konkretnych manifestacji narządowych. Wśród najczęstszych manifestacji wymienia się zajęcie górnych dróg oddechowych, nerek i płuc, [9-13]. W ciągu ostatnich dziesięcioleci doszło do znaczącego postępu w zakresie poznania mechanizmów odpowiadających za powstanie i podtrzymanie procesu chorobowego, stworzenia kryteriów klasyfikacyjnych i wyodrębnienia odmiennych fenotypów AAV, udoskonalenia metod diagnostycznych oraz wprowadzenia leczenia immunosupresyjnego. Te osiągnięcia, a zwłaszcza możliwość zastosowania glikokortykosteroidów systemowych (GKS) i innych leków immunosupresyjnych wpłynęły na poprawę rokowania chorych z AAV, powodując zmianę ich statusu ze schorzeń nieuchronnie prowadzących do szybkiego zgonu do przewlekłych chorób, przebiegających z okresami zaostrzeń i remisji [14-15]. Pomimo tego niezaprzeczalnego postępu, nadal nieznana jest etiologia AAV, nie stworzono powszechnie akceptowalnych kryteriów

diagnostycznych, optymalne schematy leczenia są wciąż poddawane weryfikacji i udoskonalane, a długo stosowana terapia immunosupresyjna staje się przyczyną licznych powikłań [16-17]. Dlatego potrzebne i uzasadnione są dalsze badania nad określeniem poszczególnych fenotypów AAV oraz analiza skuteczności i bezpieczeństwa leczenia, celem ustalenia optymalnych i zindywidualizowanych schematów terapii [14].

POLVAS

Ze względu na rzadkie występowanie jednostek z grupy AAV, zgromadzenie wystarczającej ilości danych do przeprowadzenia wiarygodnych analiz jest trudne dla pojedynczego ośrodka. Dlatego zgodnie z zaleceniami Europejskiej Komisji Ekspertów do spraw Chorób Rzadkich (EUCERD) tworzone są wieloośrodkowe rejestry, które mają na celu pozyskanie optymalnej liczby przypadków[18-19]. W 2014 r. został założony Polski Rejestr Zapaleń Naczyń (POLVAS), w ramach którego gromadzone są dane dotyczące zapaleń naczyń związanych z przeciwciałami ANCA w retrospektywnej jak i w prospektywnej części bazy [20]. Aktualnie do POLVAS należy 13 ośrodków w Polsce, wśród których II Katedra Chorób Wewnętrznych im. Prof. Andrzeja Szczeklika, Collegium Medicum, UJ jest ośrodkiem wiodącym. Rejestr POLVAS jest największą stworzoną dotychczas bazą danych obejmującą polską populację chorych na zapalenia naczyń związane z ANCA i jedną z największych tego typu baz w Europie. Zgromadzona liczba przypadków pozwala na wiarygodną analizę danych oraz umożliwia porównanie populacji polskiej z innymi kohortami oraz obowiązującymi rekomendacjami postępowania. Publikacje, wchodzące w skład niniejszej dysertacji zostały przygotowane w oparciu o dane z rejestru POLVAS.

III. CELE PRACY

Celem prowadzonych analiz było scharakteryzowanie stosowanego leczenia oraz związanych z leczeniem powikłań w polskiej populacji pacjentów z zapaleniami naczyń związanymi z ANCA na podstawie danych z retrospektywnej części rejestru POLVAS, w tym porównanie stosowanej terapii pomiędzy poszczególnymi jednostkami chorobowymi (GPA, MPA, EGPA) oraz porównanie w grupach wyodrębnionych ze względu na czas rozpoznania. Istotnym elementem pracy było przedstawienie danych dotyczących polskiej populacji w odniesieniu do aktualnych rekomendacji postępowania.

W dalszej części pracy scharakteryzowano szczególne grupy pacjentów – z zajęciem układu oddechowego oraz wymagających leczenia w oddziałach intensywnej terapii. Jako że często obejmują one przypadki o ciężkim przebiegu i gorszym niż przeciętne rokowaniu [21-25], określenie fenotypu osób należących do tych grup oraz ich skuteczne leczenie jest szczególnie ważne.

IV. METODOLOGIA

W pracy wykorzystano materiały zgromadzone w retrospektywnej części rejestru POLVAS. Do analizy zakwalifikowano 625 przypadków AAV (417 z rozpoznaniem GPA, 106 z MPA i 102 z EGPA) zgromadzonych w bazie, obejmujące chorych, u których diagnozę postawiono między 1990 a 2016 r. Dane zostały uzyskane retrospektywnie za pomocą elektronicznych kwestionariuszy.

Badania zostały przeprowadzone zgodnie z zasadami Deklaracji Helsińskiej (1964 Declaration of Helsinki). Protokół badań został zaakceptowany przez komisję etyczną Uniwersytetu Jagiellońskiego. Wszystkie ośrodki zrzeszone w POLVAS otrzymały zgody lokalnych komisji bioetycznych na prowadzenie badań.

Diagnozy poszczególnych jednostek zapaleń naczyń zostały postawione na podstawie kryteriów Amerykańskiego Towarzystwa Reumatologicznego (ACR) oraz konsensusu z Chapel Hill (2012 Chapel Hill Consensus Conference) [1, 26]. Zajęcie układu oddechowego zdefiniowano jako obecność przynajmniej jednego objawu podmiotowego, przedmiotowego, wyniku badania obrazowego albo innego stanu wskazującego na zajęcie układu oddechowego, związanego z AAV. Definicję tę spełniło 475 osób. W tej grupie wyodrębniono przypadki z radiologicznym potwierdzeniem AAV – wyselekcjonowano 316 przypadków, które poddano dalszej analizie. W rejestrze POLVAS zajęcie górnych dróg oddechowych stanowiło odrębną kategorię („ucho, nos, gardło" - ang. ENT) i objawy dotyczące zajęcia tych narządów nie były uwzględnione w kategorii zajęcia układu oddechowego. Osoby leczone w OIT zostały zakwalifikowane do analizy na podstawie kategorii, zdefiniowanej w rejestrze POLVAS jako „zaostrzenie, wymagające leczenia w OIT". Powyższe kryterium spełniło 30 osób.

Dane dotyczące charakterystyki grup, leczenia oraz związanych z leczeniem powikłań zostały poddane analizie statystycznej z użyciem standardowych metod statystyki opisowej (średnie z odchyleniem standardowym, mediany z wartością dolnego i górnego kwartyla). Celem sprawdzenia rozkładu normalnego w grupach stosowano test Shapiro-Wilk, a do oceny homogeniczności wariancji wykorzystywano test Levene'a. Porównania między grupami zostały przeprowadzone przy użyciu testów Chi^2 (z poprawkami Yates'a i Bonferroniego w razie potrzeby), testu t-studenta i/lub U Manna-Whitneya, jednoczynnikowej analizy wariancji ANOVA z testami post-hoc oraz/lub testu Kruskala-Wallisa z porównaniami par - w zależności od liczby porównań i spełnienia kryteriów dla poszczególnych testów. Wartość $p<0,05$ przyjęto za istotną statystycznie (z uwzględnieniem poprawki Bonferroniego w razie wielokrotnych porównań). Obliczenia zostały przeprowadzone przy użyciu oprogramowania StatSoft Statistica 13 software (StatStoft®, Tulsa, OK, USA) oraz SPSS Statistics (IBM®, USA).

V. WYNIKI

W pierwszej części badań scharakteryzowano leczenie i związane z leczeniem powikłania w polskiej populacji chorych na AAV.

W całej analizowanej grupie (625 przypadków AAV) średni wiek wyniósł 50,4 +/- 15,7 lat, a mediana czasu obserwacji 4,0 (2,0-8,0) lat. Stwierdzono, iż w leczeniu indukującym remisję choroby podstawowej najczęściej stosowano glikokortykosteroidy systemowe (95,3%), cyklofosfamid (78,3%) oraz rytuksymab (9,3%). Pacjenci z GPA i MPA częściej niż chorzy na EGPA otrzymywali pulsy steroidowe – definiowane jako podanie co najmniej 500 mg metyloprednizolonu i.v. w pojedynczej dawce (odpowiednio: 76,9% vs. 39,6%; $p<0,01$ oraz 78,4% vs. 39,6%; $p<0,01$), a także cyklofosfamid (odpowiednio: 85,7% vs. 43,1%; $p<0,01$ oraz 83,0% vs. 43,1%; $p<0,01$). Z kolei metotreksat i azatioprynę częściej stosowano w grupie EGPA niż GPA czy MPA (dla metotreksatu odpowiednio: 15,7% vs. 5,3%; $p<0,01$ oraz 15,7% vs. 0,9%; $p<0,01$; dla azatiopryny odpowiednio: 13,7% vs. 3,4%; $p<0,01$ oraz 13,7% vs. 1,9%; $p<0,01$). Ponadto nikt z chorujących na EGPA nie otrzymał w leczeniu indukującym rytuksymabu (przy 12,8% chorych z GPA i 4,7% z MPA leczonych rytuksymabem) ani nie był leczony plazmaferezami (przy 13,8% chorych z GPA i 15,1% z MPA leczonych plazmaferezami). W leczeniu indukującym remisję w grupie EGPA częściej niż w grupach GPA i MPA stosowano również monoterapię GKS (odpowiednio: 35,3% vs. 6,5%; $p<0,01$ oraz 35,3% vs. 14,2%; $p<0,01$). W leczeniu podtrzymującym remisję w całej grupie AAV najczęściej stosowano GKS (84,3%), azatioprynę (37,8%) i metotreksat (23,0%). Odsetek stosowanego cyklofosfamidu w leczeniu podtrzymującym remisję był znamiennie niższy wśród osób z diagnozą postawioną >2010 r. niż <2004 r. lub pomiędzy 2004-2010 r. (odpowiednio: 5,7% vs. 26,09%, $p<0,01$; i 5,7% vs. 15,9%, $p<0,01$). Mediana kumulacyjnej dawki cyklofosfamidu w całej grupie AAV wyniosła 7,99 g (4,18-14,0), była wyższa w grupie GPA (9,0 g; 5,3-16,0) niż MPA (5,0 g; 2,0-8,0) i EGPA (6,0 g; 5,4-8,58), natomiast różnice nie były istotne statystycznie po odniesieniu dawki kumulacyjnej do czasu obserwacji w poszczególnych grupach. Leczenia nerkozastępczego wymagało 21,9 % osób z AAV, najwięcej wśród chorych na MPA (MPA vs. GPA - 44,3% vs 21,5%; $p<0,01$). Nie stwierdzono konieczności leczenia nerkozastępczego w grupie EGPA. Najczęstszym powikłaniem leczenia immunosupresyjnego były infekcje – odsetek przypadków z powikłaniami infekcyjnymi wynosił 38,8%. Stwierdzono związek występowania infekcji z dłuższym czasem obserwacji (OR=1,05; 95% CI 1,00-1,10; $p=0,03$), stosowaniem pulsów GKS (OR=2,83; 95% CI 1,73-4,64; $p<0,01$) i leczeniem nerkozastępczym – dializoterapia (OR=1,73; 95% CI 1,10-2,71; $p=0,02$). Natomiast nie zaobserwowano zależności między wystąpieniem powikłań infekcyjnych, a kumulacyjną dawką

cyklofosfamidu (p=0,09). Wyniki pracy zostały opublikowane w czasopiśmie *Advances in Medical Sciences.*

W drugiej części pracy przeprowadzono analizę dotyczącą polskiej populacji AAV z zajęciem układu oddechowego.

Zajęcie układu oddechowego (z potwierdzeniem radiologicznym) stwierdzono w 68,5% przypadków całej grupy AAV, w 97,6% przypadków EGPA, 67,8% przypadków GPA oraz w 40,0% przypadków MPA. W grupie z zajęciem układu oddechowego chorujący na GPA stanowili 65,2% przypadków, MPA - 9,5% i EGPA – 25,3%. Objawom ze strony układu oddechowego towarzyszyło częstsze występowanie objawów ogólnych (89,8% vs. 80,6% w grupie bez objawów zajęcia układu oddechowego; p=0,01), zajęcie górnych dróg oddechowych (74,3% vs. 60,0%; p<0,01), objawy ze strony układu sercowo-naczyniowego (23,5% vs. 9,0%; p<0,01), zajęcie przewodu pokarmowego (16,6% vs. 7,6%; p=0,01), zajęcie centralnego systemu nerwowego (10,6% vs. 4,1%; p=0,02) i obwodowego układu nerwowego (28,8% vs. 15,9%; p<0,01). W grupie z zajęciem układu oddechowego częściej występowały zaostrzenia (mediany: 1,0 [0,0-2,0] vs. 0,0 [0,0-1,0]; p=0,01), ponadto zaobserwowano nieistotny statystycznie trend w kierunku wyższej liczby zgonów (9,0% vs. 5,8%; p=0,25), częstszych zaostrzeń wymagających hospitalizacji (48,7% vs. 41,8%; p=0,18) oraz częstszych zaostrzeń wymagających pobytu w OIT (5,1% vs. 1,4%; p=0,12). Trend ten zarysował się jeszcze wyraźniej przy analizie całej grupy spełniającej definicję zajęcia układu oddechowego wg POLVAS. Wówczas w grupach z zajęciem i bez zajęcia układu oddechowego odsetki zgonów, zaostrzeń wymagających hospitalizacji oraz zaostrzeń wymagających pobytu w OIT wynosiły odpowiednio- 10,3% vs. 5,8%, p= 0,11; 52,7% vs. 41,8%, p=0,03; 6,5% vs. 1,4%, p=0,03, osiągając istotność statystyczną dla dwóch ostatnich kategorii. Ze względu na znaczną odrębność EGPA od pozostałych jednostek klinicznych AAV, przeprowadzono również analizę obejmującą łączoną podgrupę GPA i MPA. W tej analizie grupę z zajęciem układu oddechowego (względem grupy bez zajęcia układu oddechowego) cechowały: wyższa mediana maksymalnego stężenia CRP (46,0 mg/l [14,0-105,0] vs. 25,0 mg/l [6,6-75,1]; p= 0,01), częstsze stosowanie GKS w leczeniu indukującym remisję (97,9% vs. 90,8%; p<0,01), rzadsza monoterapia (względem leczenia skojarzonego z innym lekiem immunosupresyjnym) GKS (3,4% vs. 15,5%; p<0,01), częstsze stosowanie pulsów GKS (84,1% vs. 67,7%; p<0,01), częstsza indukcja remisji z użyciem cyklofosfamidu (91,9% vs. 75,4%; p<0,01), a także częstsze wykorzystanie IVIG w leczeniu indukującym remisję (8,1% vs. 2,1%; p=0,03). W tej podgrupie (GPA+MPA) zaobserwowano również nieistotny statystycznie trend w kierunku wyższej śmiertelności chorych z zajęciem układu oddechowego (11,7% vs. 5,9%; p=0,07), który uzyskiwał istotność statystyczną po uwzględnieniu wszystkich przypadków spełniających definicję POLVAS zajęcia układu

oddechowego (12,9% vs. 5,9%; p=0,03). Wyniki pracy zostały opublikowane w czasopiśmie *Clinical and Experimental Rheumatology.*

W trzeciej części pracy dokonano charakterystyki chorych z AAV, którzy wymagali leczenia w OIT. Względem osób niewymagających pobytu w OIT, grupę tę cechowały: częstsze zajęcie układu oddechowego (93,3% vs. 74,4%; p=0,03), nerek (86,7% vs. 61,6%; p=0,01), centralnego systemu nerwowego (23,3% vs. 7,8%; p<0,01), oczu (36,7% vs. 20,1%; p=0,03), ponadto wyższa śmiertelność (53,6% vs. 7,8%; p<0,01). W tej grupie odnotowano również więcej przypadków osób z infekcjami (72,4% vs. 36,9%; p<0,01). W grupie leczonej w OIT częściej stosowano IVIG (17,2% vs. 4,8%; p<0,01) oraz częściej przeprowadzano hemodializy (48,3% vs. 21,8%; p<0,01), natomiast kumulacyjna dawka cyklofosfamidu była mniejsza niż w grupie nieleczonej w OIT (5,0 g [2,0-8,0] vs. 8,0 g [4,7-15,0]; p=0,01). W grupie AAV wymagających pobytu w OIT zwracały ponadto uwagę wyższe, choć nieistotne statystycznie, odsetki przypadków, w których stosowano cyklofosfamid (93,1% vs. 80,1%; p=0,14), rytuksymab (13,8% vs. 7,4%; p=0,36), plazmaferezy (20,7% vs. 12,1%; p=0,18) oraz pulsy GKS (82,8% vs. 73,1%; p=0,25). Wyniki pracy zostały opublikowane w czasopiśmie *Anaesthesiology Intensive Therapy.*

VI. WNIOSKI

Wnioski z przeprowadzonych badań:

1. Leczenie polskiej populacji chorych na układowe zapalenia naczyń związane z przeciwciałami przeciw cytoplazmie neutrofilów (ANCA) nie odbiegało istotnie od rekomendowanych standardów postępowania.
2. Pacjenci z eozynofilową ziarniniakowatością z zapaleniem naczyń (EGPA) byli leczeni mniej agresywnie niż osoby z GPA lub MPA, co może sugerować łagodniejszy przebieg tej jednostki chorobowej w porównaniu z pozostałymi AAV. Jakkolwiek różnice w terapii mogą być odzwierciedleniem odrębności EGPA od innych AAV, a także różnic w rekomendowanych w wytycznych schematach leczenia.
3. Rzadsze stosowanie cyklofosfamidu w leczeniu podtrzymującym remisję w podgrupach z diagnozą postawioną w późniejszych latach odzwierciedla implementację do praktyki klinicznej zmian w rekomendacjach postępowania w AAV.
4. Najczęstszym powikłaniem leczenia AAV były infekcje, których występowanie związane było z dłuższym czasem obserwacji, stosowaniem pulsów GKS i leczeniem nerkozastępczym (dializoterapia).
5. Zajęcie układu oddechowego (z radiologicznym potwierdzeniem choroby) było obecne w 68,5% polskiej populacji AAV. Najczęściej występowało w przebiegu EGPA (97,6%), następnie w GPA (67,8%), natomiast najrzadziej w MPA (40,0%). Wyniki te są porównywalne do danych z piśmiennictwa, dotyczących zajęcia układu oddechowego w AAV - co interesujące – są nieco bardziej zbliżone do kohort azjatyckich niż zachodnioeuropejskich.
6. Analiza danych dotyczących profilu pacjentów (wyższa mediana maksymalnego CRP, trend w kierunku wyższej śmiertelności) oraz stosowanego leczenia (bardziej agresywna terapia – częstsze stosowanie pulsów GKS, cyklofosfamidu w indukcji remisji, IVIG; rzadsza monoterapia GKS) sugerują cięższy przebieg GPA i MPA wśród pacjentów z zajęciem układu oddechowego w porównaniu z osobami bez zajęcia układu oddechowego.
7. Pacjentów z AAV leczonych w OIT (w porównaniu z niewymagającymi leczenia w OIT) cechowało częstsze zajęcie istotnych układów – oddechowego, nerek, CNS, a także wyższa śmiertelność.
8. Osoby z AAV, które wymagały leczenia w OIT (w porównaniu z niewymagającymi leczenia w OIT) były częściej leczone IVIG, częściej stosowano u nich także leczenie nerkozastępcze. Wartości bezwzględne wskazują również na tendencję do bardziej

agresywnego leczenia immunosupresyjnego w tej podgrupie – choć dla większości leków nie osiągnięto istotności statystycznej. Wśród pacjentów, którzy wymagali leczenia w OIT stwierdzono niższą kumulacyjną dawkę cyklofosfamidu, co jednak może być związane z wyższą śmiertelnością w tej grupie i związanym z nią krótszym czasem obserwacji.

VII. SKRÓTY

AAV – Zapalenia naczyń związane z przeciwciałami ANCA (ang. ANCA-associated vasculitides)

ACR – Amerykańskie Towarzystwo Reumatologiczne (ang. American College of Rheumatology)

ANCA - Przeciwciała przeciw cytoplazmie neutrofilów (ang. anti-neutrophil cytoplasmic antibodies)

CI – Przedział ufności (ang. confidence interval)

EGPA – Eozynofilowa ziarniniakowatość z zapaleniem naczyń (ang. eosinophilic granulomatosis with polyangiitis)

ENT – Ucho, nos, gardło (ang. ear, nose, throat)

EUCERD - Europejska Komisja Ekspertów do spraw Chorób Rzadkich (ang. European Union Committee of Experts on Rare Diseases)

GKS – Glikokortykosteroidy

GPA – Ziarniniakowatość z zapaleniem naczyń (ang. granulomatosis with polyangiitis)

i.v. - Dożylnie (ang. intravenous)

IVIG – Immunoglobuliny dożylne (ang. intravenous immunoglobulins)

MPA – Mikroskopowe zapalenie naczyń (ang. microscopic polyangiitis)

NETs – Zewnątrzkomórkowe pułapki neutrofilowe (ang. neutrophil extracellular traps)

OIT – Oddział intensywnej terapii

OR – Iloraz szans (ang. odds ratio)

POLVAS – Polski Rejestr Zapaleń Naczyń

UJ – Uniwersytet Jagielloński

VIII. STRESZCZENIE W JĘZYKU POLSKIM

Wstęp

Układowe zapalenia naczyń, związane z przeciwciałami przeciw cytoplazmie neutrofilów – ANCA (ang. ANCA-associated vasculitides; AAV) to grupa rzadkich chorób o niewyjaśnionej etiologii i autoimmunizacyjnym podłożu, do których zalicza się ziarniniakowatość z zapaleniem naczyń (ang. granulomatosis with polyangiitis; GPA), mikroskopowe zapalenie naczyń (ang. microscopic polyangiitis; MPA) oraz eozynofilową ziarniniakowatość z zapaleniem naczyń (ang. eosinophilic granulomatosis with polyangiitis; EGPA). AAV powodują zapalenie głównie drobnych naczyń, których uszkodzenie prowadzi do zmian narządowych, zależnych od dystrybucji zapalenia. Wśród najczęstszych manifestacji wymienia się zajęcie górnych dróg oddechowych, nerek i płuc, ale w przebiegu tej grupy chorób może dojść do zajęcia niemal każdego narządu. W ciągu ostatnich dziesięcioleci doszło do znaczącego postępu w zakresie diagnostyki i terapii AAV. Te osiągnięcia, a zwłaszcza możliwość zastosowania leczenia immunosupresyjnego wpłynęły na poprawę rokowania chorych z AAV, powodując zmianę ich statusu ze schorzeń nieuchronnie prowadzących do szybkiego zgonu do przewlekłych chorób, przebiegających z okresami zaostrzeń i remisji. Pomimo tego niezaprzeczalnego postępu optymalne schematy leczenia są wciąż poddawane weryfikacji i udoskonalane, a długo stosowana terapia immunosupresyjna staje się przyczyną licznych powikłań. Celem prowadzonych analiz była analiza stosowanego leczenia oraz związanych z leczeniem powikłań w polskiej populacji pacjentów z zapaleniami naczyń związanymi z ANCA. Ponadto w ramach badań scharakteryzowano szczególne grupy pacjentów – z zajęciem układu oddechowego oraz wymagających leczenia w oddziałach intensywnej terapii.

Materiały i metody

W pracy wykorzystano dane zgromadzone w retrospektywnej części rejestru POLVAS. Rejestr ten jest największą stworzoną dotychczas bazą danych obejmującą polską populację chorych na zapalenia naczyń związane z ANCA. Do oceny leczenia i związanych z leczeniem powikłań zakwalifikowano 625 przypadków AAV (417 z rozpoznaniem GPA, 106 z MPA i 102 z EGPA), obejmujące chorych, u których diagnozę postawiono między 1990 a 2016 r. Dane zostały uzyskane retrospektywnie za pomocą elektronicznych kwestionariuszy. Diagnozy poszczególnych jednostek zapaleń naczyń zostały postawione na podstawie kryteriów Amerykańskiego Towarzystwa Reumatologicznego (ACR) oraz konsensusu z Chapel Hill. Do analizy podgrupy z zajęciem układu oddechowego wyselekcjonowano 316 przypadków z radiologicznym potwierdzeniem AAV. Podgrupę osób, wymagających leczenia w OIT stworzyło 30 przypadków z bazy POLVAS, które

poddano analizie w dalszej części pracy. W ramach pracy wykorzystano statystyki opisowe oraz narzędzia statystyczne służące do porównań między grupami. Wartość $p<0,05$ przyjęto za istotną statystycznie (z uwzględnieniem poprawki Bonferroniego w razie wielokrotnych porównań).

Wyniki

W pierwszej części badań scharakteryzowano leczenie i związane z leczeniem powikłania w polskiej populacji chorych na AAV. Stwierdzono, iż w leczeniu indukującym remisję choroby podstawowej najczęściej stosowano glikokortykosteroidy systemowe (95,3%), cyklofosfamid (78,3%) oraz rytuksymab (9,3%). Pacjenci z GPA i MPA częściej niż chorzy na EGPA otrzymywali pulsy steroidowe (odpowiednio: 76,9% vs. 39,6%; $p<0,01$ oraz 78,4% vs. 39,6%; $p<0,01$), a także cyklofosfamid (odpowiednio: 85,7% vs. 43,1%; $p<0,01$ oraz 83,0% vs. 43,1%; $p<0,01$). Z kolei metotreksat, azatioprynę oraz monoterapię GKS częściej stosowano w grupie EGPA niż GPA czy MPA (dla metotreksatu odpowiednio: 15,7% vs. 5,3%; $p<0,01$ oraz 15,7% vs. 0,9%; $p<0,01$; dla azatiopryny odpowiednio: 13,7% vs. 3,4%; $p<0,01$ oraz 13,7% vs. 1,9%; $p<0,01$; dla monoterapii GKS odpowiednio: 35,3% vs. 6,5%; $p<0,01$ oraz 35,3% vs. 14,2%; $p<0,01$). Ponadto nikt z chorujących na EGPA nie otrzymał w leczeniu indukującym rytuksymabu (przy 12,8% chorych z GPA i 4,7% z MPA leczonych rytuksymabem) ani nie był leczony plazmaferezami (przy 13,8% chorych z GPA i 15,1% z MPA leczonych plazmaferezami). W leczeniu podtrzymującym remisję najczęściej stosowano GKS (84,3%), azatioprynę (37,8%) i metotreksat (23,0%). Odsetek stosowanego cyklofosfamidu w leczeniu podtrzymującym był znamiennie niższy wśród osób z diagnozą postawioną >2010 r. niż <2004 r lub pomiędzy 2004-2010 r. (odpowiednio: 5,7% vs. 26,09%, $p<0,01$; i 5,7% vs. 15,9%, $p<0,01$). Mediana kumulacyjnej dawki cyklofosfamidu w całej grupie AAV wyniosła 7,99 g (4,18-14,0). Leczenia nerkozastępczego wymagało 21,9 % osób z AAV, najwięcej wśród chorych na MPA (MPA vs. GPA - 44,3% vs 21,5%; $p<0,01$); nie stwierdzono konieczności leczenia nerkozastępczego w grupie EGPA. Najczęstszym powikłaniem leczenia immunosupresyjnego były infekcje – odsetek przypadków z powikłaniami infekcyjnymi wynosił 38,8%. Stwierdzono związek występowania infekcji z dłuższym czasem obserwacji (OR=1,05; 95% CI 1,00-1,10; $p=0,03$), stosowaniem pulsów GKS (OR=2,83; 95% CI 1,73-4,64; $p<0,01$) i leczeniem nerkozastępczym (OR=1,73; 95% CI 1,10-2,71; $p=0,02$).

W drugiej części pracy przeprowadzono analizę dotyczącą polskiej populacji AAV z zajęciem układu oddechowego. Zajęcie układu oddechowego (z potwierdzeniem radiologicznym) stwierdzono w 68,5% wszystkich przypadków AAV, 97,6% przypadków EGPA, 67,8% przypadków GPA oraz w 40,0% przypadków MPA. Objawom ze strony układu oddechowego towarzyszyło częstsze występowanie objawów ogólnych, zajęcie górnych dróg oddechowych,

układu sercowo-naczyniowego, przewodu pokarmowego, centralnego systemu nerwowego i obwodowego układu nerwowego. W grupie z zajęciem układu oddechowego częściej występowały zaostrzenia (mediany: 1,0 [0,0-2,0] vs. 0,0 [0,0-1,0]; p=0,01), ponadto zaobserwowano nieistotny statystycznie trend w kierunku wyższej liczby zgonów (9,0% vs. 5,8%; p=0,25), częstszych zaostrzeń wymagających hospitalizacji (48,7% vs. 41,8%; p=0,18) oraz częstszych zaostrzeń wymagających pobytu w OIT (5,1% vs. 1,4%; p=0,12). W analizie łączonej podgrupy GPA i MPA (z wyłączeniem EGPA) grupę z zajęciem układu oddechowego (względem grupy bez zajęcia układu oddechowego) cechowały: wyższa mediana maksymalnego stężenia CRP (46,0 mg/l [14,0-105,0] vs. 25,0 mg/l [6,6-75,1]; p= 0,01), częstsze stosowanie GKS w leczeniu indukującym remisję (97,9% vs. 90,8%; p<0,01), rzadsza monoterapia GKS (3,4% vs. 15,5%; p<0,01), częstsze stosowanie pulsów GKS (84,1% vs. 67,7%; p<0,01), częstsza indukcja remisji z użyciem cyklofosfamidu (91,9% vs. 75,4%; p<0,01), a także częstsze wykorzystanie IVIG w leczeniu indukującym remisję (8,1% vs. 2,1%; p=0,03).

W trzeciej części pracy dokonano charakterystyki chorych z AAV, którzy wymagali leczenia w OIT. Względem osób niewymagających pobytu w OIT, grupę tę cechowały: częstsze zajęcie układu oddechowego, nerek, centralnego systemu nerwowego, oczu. Ponadto w tej grupie odnotowano więcej przypadków osób z infekcjami (72,4% vs. 36,9%; p<0,01) oraz wyższą śmiertelność (53,6% vs. 7,8%; p<0,01). W grupie leczonej w OIT częściej stosowano IVIG (17,2% vs. 4,8%; p<0,01) oraz częściej przeprowadzano hemodializy (48,3% vs. 21,8%; p<0,01).

Wnioski

Leczenie polskiej populacji chorych na AAV nie odbiegało istotnie od rekomendowanych standardów postępowania i odzwierciedlało zmiany w wytycznych. Pacjenci z EGPA byli leczeni mniej agresywnie niż osoby z GPA lub MPA, co może sugerować łagodniejszy przebieg tej jednostki chorobowej w porównaniu z pozostałymi AAV. Najczęstszym powikłaniem leczenia AAV były infekcje, których występowanie związane było z dłuższym czasem obserwacji, stosowaniem pulsów GKS i leczeniem nerkozastępczym. Zajęcie układu oddechowego (z radiologicznym potwierdzeniem choroby) było obecne w 68,5 % polskiej populacji AAV - najczęściej w przebiegu EGPA (97,6%), następnie w GPA (67,8%), najrzadziej w MPA (40,0%). Profil pacjentów oraz bardziej agresywne leczenie w łączonej podgrupie GPA i MPA sugeruje cięższy przebieg tych chorób wśród osób z zajęciem układu oddechowego w porównaniu z osobami bez zajęcia układu oddechowego. Pacjentów z AAV leczonych w OIT (w porównaniu z niewymagającymi leczenia w OIT) cechowało częstsze zajęcie istotnych układów – oddechowego, nerek, CNS, częstsze występowanie infekcji a także wyższa śmiertelność. Leczenie w tej grupie wskazuje na trend w

kierunku stosowania bardziej intensywnego leczenia immunosupresyjnego.

Słowa kluczowe

Zapalenia naczyń związane z ANCA, GPA, MPA, EGPA, Leczenie immunosupresyjne, Zajęcie układu oddechowego

IX. STRESZCZENIE W JĘZYKU ANGIELSKIM

Introduction

ANCA-associated vasculitides (AAV) is a group of rare diseases of unknown etiology and autoimmune patomechanism, which includes three entities - granulomatosis with polyangiitis (GPA), microscopic polyangiitis, (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). AAV cause predominantly inflammation of the small vessels, which damage leads to the organ lesions, depending on the distribution of the inflammatory changes. Among the most common manifestations there are ENT, renal and pulmonary involvement, however, almost each organ may be involved in the course of this group of diseases. The significant advancement in the field of diagnostics and therapy of AAV have been made during the last several decades. These achievements, especially the possibility of administration of the immunosuppressive treatment have resulted in the improvement of the outcomes for patients with AAV, changing the status of these disorders from rapidly progressive and inevitably fatal to chronic, relapsing diseases. Despite this undeniable progress, the optimal treatment regimens are still being discussed and revised and long-lasting immunosuppressive treatment have become an important factor influencing mortality and morbidity. The aim of the study was the analysis of the treatment modalities and the associated side effects in a Polish nation-wide ANCA-associated vasculitides (AAV) patients' cohort. Moreover, the particular subgroups have been characterised – the patients with respiratory involvement and the group which needed stay at intensive care unit (ICU).

Materials and methods

The data from retrospective branch of POLVAS registry have been used in this study. POLVAS is to date the largest ever created database, encompassing Polish population of AAV. Six hundred and twenty-five cases (417 with GPA, 106 with MPA and 102 with EGPA), with the diagnoses established between 1990 and 2016 years, were qualified for the assessment of the treatment and treatment-associated side effects. The data were obtained using retrospective questionnaires. The diagnoses of the particular entities were based on the American College of Rheumatology (ACR) criteria and 2012 Revised International Chapel Hill Consensus criteria. Three hundred and sixteen cases with radiological confirmation of AAV presence were selected for the analysis of the subgroup with respiratory involvement. Thirty cases from POLVAS database were included in the subgroup of AAV patients, who needed ICU stay and were analysed in the further part of the study. Standard descriptive statistics and statistic tools made for performing comparisons between groups were used. P-value <0.05 was assumed as statistically significant (modified with Bonferroni

correction when multiple comparisons were performed).

Results

Treatment and treatment-associated side effects in the Polish population of AAV were characterised in the first part of the analyses.

The most frequently used medicaments in the remission induction treatment were glucocorticosteroids (GCS; 95.3%), cyclophosphamide (78.3%) and rituximab (9.3%). Patients with GPA and MPA were administered steroid pulses more frequently than those with EGPA (76.9% vs. 39.6%, $p<0.01$ and 78.4% vs. 39.6%, $p<0.01$, respectively), as well as cyclophosphamide (85.7% vs. 43.1%; $p<0.01$ and 83.0% vs. 43,1% $p<0.01$, respectively). On the other hand, methotrexate, azathioprine and GCS monotherapy were used more often in the EGPA group than GPA or MPA groups (for methotrexate: 15.7% vs. 5.3%, $p<0.01$ and 15.7% vs. 0.9%, $p<0.01$, respectively; for azathioprine: 13.7% vs. 3.4%, $p<0.01$ and 13.7% vs. 1.9%, $p<0.01$, respectively; for GCS monotherapy: 35.3% vs. 6.5%, $p<0.01$ and 35.3% vs. 14.2%, $p<0.01$, respectively). Moreover, there was no case of rituximab nor plasmaphereses use during the remission induction phase in EGPA patients (compared to 12.8% cases of GPA and 4.7% cases of MPA with rituximab use as well as 13.8% cases of GPA and 15.1% cases of MPA with plasmaphereses use). Glucocorticosteroids, azathioprine and methotrexate were the most frequently administered drugs during maintenance therapy (the proportions in the whole group equalled to 84.3%, 37.8% and 23.0%, respectively). The proportion of cyclophosphamide use during the maintenance treatment was significantly lower in the cases with diagnosis established after 2010, compared to those with diagnosis made before 2004 or between 2004 and 2010 years (5.7% vs. 26.09%, $p<0.01$ and 5.7% vs. 15.9%, $p<0.01$, respectively). The median cumulative dose of cyclophosphamide equalled 7.99g (4.18-14.0). Renal replacement therapy was required in 21.9% of all AAV cases. MPA patients predominated among patients requiring dialysis (MPA vs. GPA - 44.3% vs. 21.5%, $p<0.01$). None of EGPA patients needed renal replacement therapy. The most common adverse effect of immunosuppressive treatment were infections – proportion of cases equalled 38.8% of the whole group. The infections' occurrence was associated with longer average observation time (OR=1.05, 95% CI 1.00-1.10, p=0.03), GCS pulses administration (OR=2.83, 95% CI 1.73-4.64, $p<0.01$) and renal replacement therapy (OR=1.725, 95% CI 1.10-2.71, p=0.02).

The analysis, regarding Polish population of AAV with respiratory involvement was performed in the second part of the study. The prevalence of respiratory involvement (with radiological confirmation) amounted to 68.5% of all AAV cases, 97.6% of EGPA cases, 67.8% of GPA cases and 40.0% of MPA cases. Constitutional symptoms, ENT, cardiovascular, gastrointestinal, central and

peripheral nervous system involvement were reported more frequently in the group with respiratory involvement than in the group without such manifestation. The overall number of relapses was significantly higher in the group with respiratory involvement (medians: 1.0 [0.0-2.0] vs. 0.0 [0.0-1.0], p=0.01). Moreover, statistically insignificant trends towards higher mortality (9.0% vs. 5.8%, p=0.25), more frequent relapses requiring hospitalisation (48.7% vs. 41.8%, p=0.18) and ICU stay (5.1% vs. 1.4%, p=0.12) in this group were noticed. In the analysis of the combined group of GPA and MPA cases (EGPA cases excluded), the subgroup with respiratory involvement (compared to the subgroup without respiratory involvement) was characterised by higher median, maximal CRP concentration (46.0 mg/l [14.0-105.0] vs. 25.0 mg/l [6.6-75.1], p= 0.01), more frequent GCS use in remission induction (97.9% vs. 90.8%, p<0.01), rarer GCS monotherapy (3.4% vs. 15.5%, p<0.01), more frequent GCS pulses use (84.1% vs. 67.7%, p<0.01), more frequent cyclophosphamide administration during remission induction phase (91.9% vs. 75.4%, p<0.01) and more frequent IVIG use (8.1% vs. 2.1%, p=0.03).

The description of cases with AAV who needed ICU stay was made in the third part of the study.

More frequent respiratory, renal, central nervous system and eye involvement were observed in this group in comparison with the subgroup of cases who did not require ICU stay. In addition, more cases with infections (72.4% vs. 36.9%, p<0.01) and higher mortality were present in the group which needed stay in ICU (53.6% vs. 7.8%, p<0.01). IVIG treatment and hemodialysis were used more frequently in the group requiring ICU stay (17.2% vs. 4.8%, p<0.01 and 48.3% vs. 21.8%, p<0.01, respectively).

Conclusions

The treatment of Polish patients with AAV was predominantly in line with appropriate recommendations and reflected the changes in the guidelines. EGPA cases were treated less aggressively than GPA or MPA cases, which may suggest milder course of this entity in comparison with the other AAV. The most frequent side effect of the treatment were infections, which occurrence was associated with longer observation period, GCS pulses administration and renal replacement therapy. The prevalence of respiratory involvement (with radiological confirmation) amounted to 68.5% of all AAV cases and was highest in EGPA cases (97.6%), followed by GPA cases (67.8%) and MPA cases (40.0%). Patients' profile and more aggressive treatment in the combined GPA and MPA group suggest more severe course of disease in cases with respiratory involvement compared to the subgroup without pulmonary manifestations. AAV cases treated in ICU (compared to those not requiring ICU stay) were characterised by more frequent involvement of crucial systems – respiratory, renal, CNS, more frequent infectious complications as well as

higher mortality. Treatment regimens in this subgroup indicate the trend towards more intensive immunosuppressive therapy administration.

Keywords

ANCA-associated vasculitides, GPA, MPA, EGPA, immunosuppressive treatment, respiratory involvement

X. PIŚMIENNICTWO

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013;65 1: 1-11.
2. Berti, A. and C. Dejaco: Update on the epidemiology, risk factors, and outcomes of systemic vasculitides. Best Pract Res Clin Rheumatol 2018; 32(2): 271-94.
3. Watts RA, Lane S, Scott DG. What is known about the epidemiology of the vasculitides? Best Pract Res Clin Rheumatol 2005;19 2: 191-207.
4. Chen, M., Kallenberg, C. ANCA-associated vasculitides—advances in pathogenesis and treatment. *Nat Rev Rheumatol* **6,** 653–664 (2010).
5. Jennette JC, Falk RJ. Pathogenesis of antineutrophil cytoplasmic autoantibody-mediated disease. Nat Rev Rheumatol. 2014 Aug;10(8):463-73.
6. Xiao H, Hu P, Falk RJ, Jennette JC. Overview of the Pathogenesis of ANCA-Associated Vasculitis. Kidney Dis (Basel). 2016 Mar;1(4):205-15.
7. Nakazawa D, Masuda S, Tomaru U, Ishizu A. Pathogenesis and therapeutic interventions for ANCA-associated vasculitis. Nat Rev Rheumatol. 2019 Feb;15(2):91-101.
8. Vaglio, A., C. Buzio, and J. Zwerina: Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): state of the art. Allergy 2013; 68(3): 261-73.
9. Guillevin, L., B. Durand-Gasselin, R. Cevallos, et al.: Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. Arthritis Rheum 1999; 42(3): 421-30.
10. Lane, S.E., R.A. Watts, L. Shepstone, and D.G. Scott: Primary systemic vasculitis: clinical features and mortality. QJM 2005; 98(2): 97-111.
11. Gioffredi A, Maritati F, Oliva E, Buzio C. Eosinophilic granulomatosis with polyangiitis: An overview. Front Immunol. 2014;5(NOV):1–8.
12. Solans-Laque, R., G. Fraile, M. Rodriguez-Carballeira, et al.: Clinical characteristics and outcome of Spanish patients with ANCA-associated vasculitides: Impact of the vasculitis type, ANCA specificity, and treatment on mortality and morbidity. Medicine (Baltimore) 2017; 96(8): e6083.
13. Sharma, A., G. Naidu, M. Rathi, et al.: Clinical features and long-term outcomes of 105 granulomatosis with polyangiitis patients: A single center experience from north India. Int J Rheum Dis 2018; 21(1): 278-84.
14. Chung SA, Langford CA, Maz M, Abril A, Gorelik M, Guyatt G et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of

Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Care Res (Hoboken). 2021 Aug;73(8):1088-1105.

15. Yates M, Watts R. ANCA-associated vasculitis.Clin Med (Lond). 2017;17(1):60-64.
16. Flossmann O. Risks of treatments and long-term outcomes of systemic ANCA-associated vasculitis. Presse Med 2015;44 6 Pt 2: e251-7.
17. Wall N, Harper L. Complications of long-term therapy for ANCA-associated systemic vasculitis. Nat Rev Nephrol 2012;8 9: 523-32.
18. Gliklich RE, Dreyer NA, Leavy MB, editors. Registries for Evaluating Patient Outcomes: A User's Guide [Internet]. 3rd ed. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Apr. Report No.: 13(14)-EHC111.
19. https://rarediseases.org/wp-content/uploads/2015/12/EUCERD_Recommendations_RDRegistryDataCollection_adopted.pdf
20. Musial J, Wojcik K. Polish Vasculitis Registry: POLVAS. Pol Arch Intern Med 2017;127 1: 71-2.
21. Thickett, D.R., A.G. Richter, N. Nathani, G.D. Perkins, and L. Harper: Pulmonary manifestations of anti-neutrophil cytoplasmic antibody (ANCA)-positive vasculitis. Rheumatology (Oxford) 2006; 45(3): 261-8.
22. Lai, Q.Y., T.T. Ma, Z.Y. Li, D.Y. Chang, M.H. Zhao, and M. Chen: Predictors for mortality in patients with antineutrophil cytoplasmic autoantibody-associated vasculitis: a study of 398 Chinese patients. J Rheumatol 2014; 41(9): 1849-55.
23. Alba, M.A., L.F. Flores-Suarez, A.G. Henderson, et al.: Interstital lung disease in ANCA vasculitis. Autoimmun Rev 2017; 16(7): 722-9.
24. Demiselle, J., J. Auchabie, F. Beloncle, et al.: Patients with ANCA-associated vasculitis admitted to the intensive care unit with acute vasculitis manifestations: a retrospective and comparative multicentric study. Ann Intensive Care 2017; 7(1): 39.
25. Wludarczyk, A., K. Polok, J. Gorka, et al.: Patients with small-vessel vasculitides have the highest mortality among systemic autoimmune diseases patients treated in intensive care unit: A retrospective study with 5-year follow-up. J Crit Care 2018; 48: 166-71.
26. Bloch DA, Michel BA, Hunder GG, McShane DJ, Arend WP, Calabrese LH et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Patients and methods. Arthritis Rheum 1990;33 8: 1068-73.

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Treatment and its side effects in ANCA-associated vasculitides – Study based on POLVAS registry data

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ABSTRACT

Purpose: The aim of this study is to present the treatment modalities and associated side effects in a Polish nation-wide ANCA-associated vasculitides (AAV) patients' cohort.

Materials and methods: Retrospective analysis of patients diagnosed with AAV between 1990 and 2016, included in the POLVAS registry was performed. Standard descriptive statistic methods were used with an emphasis on the treatment modalities.

Results: There were 625 patients diagnosed with AAV included in this study: 417 cases of granulomatosis with polyangiitis (GPA; 66.7%), 106 cases of microscopic polyangiitis (MPA; 17.0%) and 102 cases of eosinophilic granulomatosis with polyangiitis (EGPA; 16.3%). The mean age at the date of diagnosis was 50.4 (± 15.7) years and the median observational period amounted to 4.0 (2.0–8.0) years.

Glucocorticosteroids (GCs) were the medicaments most frequently used for remission induction (593/622; 95.3%), followed by cyclophosphamide (487/622; 78.3%), rituximab (44/622; 7.1%), and methotrexate (39/622; 6.3%). GCs were also most frequently administered for maintenance therapy (499/592; 84.3%), followed by azathioprine (224/592; 37.8%), methotrexate (136/592; 23.0%) and mycophenolate mofetil (99/592; 16.7%). The median cumulative doses of cyclophosphamide and rituximab equalled 7.99 g (4.18–14.0) and 2000 mg (1500–2800), respectively. The most commonly observed adverse events included: infections - 214/551 cases (38.8%), which were associated with the time of observation (OR = 1.05; 95% CI 1.01–1.10), the use

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of GCs intravenous pulses (OR = 2.76; 95% CI 1.68–4.54) and need for haemodialysis (OR = 1.73; 95% CI 1.10–2.71).
Conclusions: Polish patients with AAV were predominantly treated according to appropriate guidelines. The most frequent adverse events were typical for usually administered immunosuppressive treatment.

1. Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a group of rare, autoimmune diseases, affecting predominantly small vessels. According to the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides, the group of AAV consists of three distinct entities, namely, granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) [1]. The annual incidence of these diseases is estimated to be 4.9–10.2 per million for GPA, 2.7–11.6 per million for MPA and 0.5–4.2 per million for EGPA [2]. Since glucocorticosteroids and the other immunosuppressive drugs were introduced for the management of AAV, the outcomes for the sufferers have significantly improved and these disorders have changed their status from rapidly progressive and inevitably fatal conditions to chronic, relapsing diseases, if early diagnosed and properly treated. Despite this undeniable progress, the optimal treatment regimens are still being discussed and revised, with relevant difficulties related to the rarity of the diseases and scarcity of the large clinical trials. Moreover, due to generally better prognosis, the short and long-term complications of the treatment have become an important factor influencing mortality and morbidity. For these reasons, search for optimal treatment regimens, tailored for distinct subsets of AAV, and careful monitoring of possible side effects are warranted.

1.1. POLVAS

Due to the rarity of AAV, it is impossible for a single centre to design and pursue prospective, randomized, clinical trials regarding management. Therefore, multi-center databases – called Rare Diseases Registries (RDRs) - are recommended by the European Union Committee of Experts on Rare Diseases (EUCERD) [3].In 2014, the Consortium of the Polish Vasculitis Registry (POLVAS) was established [4], consisting of both retrospective and prospective branches of the registry. The aim of this study is to present the treatment modalities and associated side effects among the patients of Polish population with AAV registered in the retrospective part of POLVAS database.

2. Material and methods

2.1. Methods

In the retrospective part of POLVAS database, 625 cases of AAV were included, encompassing patients diagnosed with AAV from 1990 to 2016, who stayed under the care of POLVAS affiliated centers. The POLVAS registry structure was described elsewhere [4,5]. The medical history of the participants was analysed retrospectively and the data regarding treatment protocols, adverse effects and complications were collected using electronic questionnaires. All cases of AAV available in the documentation gathered in POLVAS affiliated centers were included into retrospective part of POLVAS.

The vasculitides diagnoses were made according to the American College of Rheumatology (ACR) classification and 2012 Revised International Chapel Hill Consensus criteria [1,6].

Additionally, AAV patients were subdivided into 3 subgroups according to the time when definite diagnosis was established, i.e. 1) before 2004, 2) between 2004 and 2010, and 3) after 2010). The division was based on the time of publishing the results of breakthrough researches - CYCAZAREM in 2003, and RAVE and RITUXIVAS both in 2010 [7–9] – which significantly influenced treatment regimens in AAV.

2.2. Ethical issues

The study was carried out in accordance with The Code of Ethics of the World Medical Association (1964 Declaration of Helsinki). The study protocol was approved by Jagiellonian University Bioethics Committee (Poland), approval No. 122.6120.25.2016. All POLVAS sites acquired local ethics committee approval before starting the recruitment.

2.3. Statistical analysis

Standard descriptive statistics were used. Normal distribution of variables was checked by Shapiro-Wilk test, and Levene's test served to assess homogeneity of variances. To compare the studied groups $\chi 2$ test (with Yates correction if needed) was used. Univariate ANOVA with post-hoc test was performed for comparisons of normally distributed variables and Kruskal-Wallis test with pairwise comparisons or Mann-Whitney *U* test were carried out for comparisons of non-normally distributed variables. Binary logistic regression was used for assessment of the odds ratios of distinct variables. The p-value < 0.05 was assumed as statistically significant, modified with Bonferroni correction when multiple comparisons were performed. Calculations were performed with StatSoft Statistica 13 software (StatSoft®, Tulsa, OK, USA) and SPSS Statistics (IBM®, USA).

Table 1
Basic description of the group.

	All	GPA	MPA	EGPA	p-value[a]		
No. of cases (N)	625	417 (66.7%)	106 (17.0%)	102 (16.3%)	–		
Men	298 (47.7%)	210 (50.4%)	54 (50.9%)	34 (33.3%)	0.1009		
Mean age (years)	50.4 ± 15.7	49.0 ± 15.3	**61.5 ± 13.8**	44.8 ± 14.4	**< 0.0001**		
Median observation (years)	4.0 (2.0–8.0)	5.0 (2.0–8.0)	2.0 (1.0–4.0)	5.5 (3.0–10.0)	**0.0206**		
Deaths	56 (8.96%)	42 (10.07%)	13 (12.26%)	1 (0.98%)	GPA vs MPA	GPA vs EGPA	MPA vs EGPA
					0.5112	**0.0053**	**0.0030**
Cases with at least one relapse[b]	340 (54.9%)	243 (58.8%)	27 (25.5%)	70 (70.0%)	GPA vs MPA	GPA vs EGPA	MPA vs EGPA
					< 0.0001	**0.0400**	**< 0.0001**

Statistically significant p-values are **bolded**.
[a] P-value is evaluated for the group of all cases. $\chi 2$ and Kruskal-Wallis tests were used (assumed level of significance = 0.05).
[b] There were 6 cases with no available data in this analysis – 4 cases of GPA and 2 cases of EGPA.

3. Results

3.1. Group description

Six hundred and twenty-five patients were qualified to this study (all patients included in the retrospective POLVAS database). Among them, there were 417 cases of GPA (66.7%), 106 cases of MPA (17.0%) and 102 cases of EGPA (16.3%). The median time of observation (defined as the difference between the date of inclusion to the database and the date of establishment of the diagnosis) equalled 4.0 (2.0–8.0) years with the shortest observation in MPA (2.0; 1.0–4.0 years). Basic demographic characteristics are presented in Table 1. There were 469 ANCA positive patients, 62 ANCA negative patients (mostly in EGPA group) and 94 had unknown ANCA status. Detailed immunological profile of included subjects is presented in the Supplementary Table s1.

3.2. Treatment - remission induction

Remission induction treatment was defined as the therapy used either until remission achievement or during the first six months of treatment, if the remission was not achieved. Glucocorticosteroids (GCs) were the drugs most frequently used for remission induction therapy. There was no statistical difference in GCs use between AAV groups. GCs pulses, defined as administering 500 mg or more methylprednisolone (or other GCs in equivalent dose) in a single intravenous (i.v.) infusion were used in 378 cases (378/513; 73.7%). Patients with GPA, as well as those with MPA were administered GCs pulses more frequently than patients diagnosed with EGPA (283/368, 76.9% vs. 19/48, 39.6%; $p < 0.0001$ and 76/97, 78.4% vs. 19/48, 39.6%; $p < 0.0001$, respectively).

The second immunosuppressive agent most frequently used for remission induction was cyclophosphamide (487 cases; 78.3%), followed by rituximab (58 cases; 9.3%). Cyclophosphamide was used significantly more often in GPA and MPA than in EGPA (355/414, 85.7% vs. 44/102, 43.1%; $p < 0.0001$ and 88/106, 83.0% vs. 44/102, 43.1%; $p < 0.0001$, respectively). Rituximab was used more frequently in GPA than in MPA (53/414, 12.8% vs. 5/106, 4.7%; $p < 0.02$). None of the patients with EGPA received rituximab for remission induction treatment.

On the contrary, the use of methotrexate, as well as azathioprine was significantly more frequent in EGPA comparing to GPA and to MPA (methotrexate: 16/102, 15.7% vs. 22/414, 5.3%; $p = 0.0003$ and 16/102, 15.7% vs. 1/106, 0.9%; $p = 0.0003$, respectively; azathioprine: 14/102, 13.7% vs. 14/414, 3.4%; $p < 0.0001$ and 14/102, 13.7% vs. 2/106, 1.9%; $p = 0.0033$, respectively). More detailed information is presented in Table 2.

3.3. Renal replacement therapy

Haemodialysis was required in 134 (21.9%) of all AAV cases during the analysed period. Ninety one patients (14.8%) required haemodialysis permanently while 43 (7.0%) were hemodialyzed temporarily during the course of the disease. None of EGPA patients needed renal replacement therapy. MPA patients predominated among patients requiring dialysis (47/106, 44.3% vs. 87/405, 21.5%; $p < 0.001$). The details are presented in Table 3. Among the patients who needed renal replacement therapy, the only significant difference between temporarily and permanently hemodialyzed was the age ($p = 0.002$; medians - 60 and 54 years, respectively.) The details are presented in the Supplementary Table s2.

3.4. Treatment – maintenance therapy

Maintenance treatment was defined as the therapy after remission achievement or after the first 6 months of treatment, if the remission was not achieved. GCs were used for maintenance therapy in 499 cases (84.3%). In most cases with available data, GCs were used for the whole time of observation (median = 100.0% (70.0–100.0)).Other immunosuppressive drugs used frequently for maintenance therapy were: azathioprine (224 cases; 37.8%), methotrexate (136 cases; 23.0%), mycophenolate mofetil (99 cases; 16.7%) and cyclophosphamide (70 cases; 11.8%). No maintenance treatment was used in 36 cases (6.1%). Azathioprine was administered more frequently to GPA patients than to MPA (162/402, 40.3% vs. 23/103, 22.3%; $p = 0.0007$) and also significantly more frequently in EGPA as compared to MPA (39/87, 44.8% vs. 23/103, 22.3%; $p = 0.0010$). Similarly, methotrexate was used more frequently in GPA comparing with MPA (104/402, 25.9% vs. 8/103, 7.8%; $p = 0.0001$) and again administered more frequently in EGPA as compared with MPA (24/87, 27.6% vs. 8/103, 7.8%; $p = 0.0003$). The details are presented in Table 4.

Table 2
Treatment use for remission induction.

	All	GPA	MPA	EGPA	GPA/MPA	GPA/EGPA	MPA/EGPA
GCs use (all forms of administration) #	593 (95.3%)	388 (93.7%)	104 (98.1%)	101 (99.0%)	0.1219	0.0568	0.9732
GCs only orally	123 (19.8%)	75 (18.1%)	15 (14.2%)	33 (32.4%)	0.3356	**0.0015**	**0.0018**
GCs only intravenously	187 (30.1%)	124 (30.0%)	60 (56.6%)	3 (2.9%)	**< 0.0001**	**< 0.0001**	**< 0.0001**
GCs both orally and intravenously	281 (45.2%)	187 (45.2%)	29 (27.4%)	65 (63.7%)	**0.0009**	**0.0008**	**< 0.0001**
GCs without any other immunosuppressive drug	78 (12.5%)	27 (6.5%)	15 (14.2%)	36 (35.3%)	**0.0101**	**< 0.0001**	**0.0004**
GCs pulses used (at least 1)	378† (73.7%)	283 ‡ (76.9%)	76 § (78.4%)	19 (39.6%)	0.5068	**< 0.0001**	**< 0.0001**
No GCs	29 (4.7%)	26 (6.3%)	2 (1.9%)	1 (1.0%)	0.1219	0.0568	**0.9732**
CYC #	487 (78.3%)	355 (85.7%)	88 (83.0%)	44 (43.1%)	0.4801	**< 0.0001**	**< 0.0001**
RTX #	58 (9.3%)	53 (12.8%)	5 (4.7%)	0 (0.0%)	**0.0183**	-	-
MTX #	39 (6.3%)	22 (5.3%)	1 (0.9%)	16 (15.7%)	0.0914	**0.0003**	**0.0003**
AZA #	30 (4.8%)	14 (3.4%)	2 (1.9%)	14 (13.7%)	0.6312	**< 0.0001**	**0.0033**
MMF #	5 (0.8%)	3 (0.7%)	0 (0.0%)	2 (2.0%)	-	0.5637	-
IVIG #	31 (5.0%)	26 (6.3%)	3 (2.8%)	2 (2.0%)	0.2527	0.1386	**0.9653**
Plasmaphereses +	72 (11.7%)	56 (13.8%)	16 (15.1%)	0 (0.0%)	0.7385	-	-

No data in 3 cases of GPA; † 513 cases available for GCs pulses analysis; ‡ 368 cases available for GCs pulses analysis; § 97 cases available for GCs pulses analysis; ¶ 48 cases available for GCs pulses analysis.
+ No data in 12 cases of GPA.
Additionally, 2 cases of GCs use in unknown form, 2 cases of cyclosporine use, 1 case of sulfasalazine use and 1 case of chloroquine use in induction remission.
Assumed statistical significance level of $\chi 2$ test (with Yates correction if needed) = 0.05, adjusted with Bonferroni correction if multiple comparisons performed = 0.017.
Statistically significant p-values are **bolded**.
Abbreviations: GCs = glucocorticoids; CYC = cyclophosphamide; RTX = rituximab; MTX = methotrexate; AZA = azathioprine; MMF = mycophenolate mofetil; IVIG = intravenous immunoglobulins.

Table 3
Renal replacement therapy.

	All	GPA	MPA	EGPA	GPA/MPA * (p-value)
No. of cases (N)	613	405	106	102	–
Haemodialysis (totally)	134 (21.9%)	87 (21.5%)	47 (44.3%)	0 (0.0%)	**< 0.0001**
Haemodialysis temporarily	43 (7.0%)	32 (7.9%)	11 (10.4%)	0 (0.0%)	0.4136
Haemodialysis permanently/End stage renal disease	91 (14.8%)	55 (13.6%)	36 (34.0%)	0 (0.0%)	**< 0.0001**

Assumed statistical significance level of $\chi 2$ test (with Yates correction if needed) = 0.05.
Comparison was performed only between GPA and MPA group, as there was no case of EGPA who needed renal replacement therapy.
Statistically significant p-values are **bolded**.

3.5. Cumulative immunosuppressive drug doses

The median cumulative dose of cyclophosphamide equalled 7.99 g (4.18–14.0). The highest amount of cyclophosphamide was administered to GPA patients (9.0 g; 5.3–16.0). The median cumulative dose of cyclophosphamide adjusted for a year of observation equalled 2.65 g/year with no statistically significant differences between the subgroups (GPA, MPA, EGPA). There were 46 cases (46/493; 9.33%), in which the cumulative dose of 25 g was exceeded, mainly diagnosed with GPA. The median cumulative dose of rituximab equalled 2000 mg (1500–2800).

More details are available in the Supplementary Table s3 and Supplementary Table s4.

3.6. Differences in AAV patients diagnosed in different time periods

The analysis of AAV group, based on the time of diagnosis was performed. The lowest use of cyclophosphamide as the maintenance treatment was in the group diagnosed after 2010 (20//351; 5.70%), comparing to the group with diagnosis made before 2004 (18/69; 26.09%; $p < 0.0001$) and group diagnosed between 2004 and 2010 (31/195; 15.90%; $p = 0.0001$). The use of azathioprine and methotrexate was also lower in patients diagnosed in the most recent period than in the earlier periods ($p = 0.0004$ and 0.0115 for azathioprine use and methotrexate use, respectively). The details are presented in Fig. 1 and in the Supplementary Table s5. The rate of adverse events as related to the time period when the AAV diagnosis was established is displayed in Fig. 1.

3.7. Adverse events

Adverse events occurred in 377 of AAV patients with infections being the most common. The definitions of adverse events were based mainly on clinical assessment (more detailed information with full list of side effects is provided in the Supplementary Table s6. All mentioned cases of infections in the medical documentation were considered as relevant. Patients who developed infections were characterized by the longer average observation time (median 4.75 years vs. 2.75 years; $p = 0.034$; OR = 1.05; 95% CI 1.00–1.10). Also, they more often received GCs pulses (at least one pulse vs. no pulses; 75.2% vs. 61.7%; $p < 0.001$; OR = 2.83; 95% CI 1.73–4.64) and more frequently needed haemodialysis (29.38% vs. 18.37%; $p = 0.018$; OR = 1.725; 95% CI 1.10–2.71). Cumulative cyclophosphamide dose was not associated with occurrence of infections ($p = 0.092$). The detailed data are presented in Table 5.

3.8. Relapses and mortality

The highest proportion of patients who developed relapses was in the EGPA subgroup. In the analysis, regarding cumulative number of relapses in our AAV population, the association with infections was found ($p = 0.0002$; results obtained using linear regression model). No factors were revealed to be associated with the occurrence of relapses which required hospitalisation. More information concerning relapses is available in Table 1.

There were 56 deaths among all patients with AAV (8.96%). The mortality rate was similar in GPA and MPA groups (10.07% and 12.26%, respectively; $p = 0.5112$), whereas only 1 patient diagnosed with EGPA died (0.98%). Treatment related factors associated with death were: need for haemodialysis ($p < 0.0001$) and steroid pulse use ($p = 0.0425$). The more detailed description of mortality among the cases gathered in the POLVAS retrospective database is presented in another publication [10].

Table 4
Immunosuppressive drugs used among those who received maintenance therapy.

	All	GPA	MPA	EGPA	GPA/MPA (p-value)	GPA/EGPA (p-value)	MPA/EGPA (p-value)
No. of cases (N)	592	402	103	87	–	–	–
GCs	499 (84.3%)	333 (82.8%)	86 (83.5%)	80 (92.0%)	0.8738	0.0333	0.0804
AZA	224 (37.8%)	162 (40.3%)	23 (22.3%)	39 (44.8%)	**0.0007**	0.4363	**0.0010**
MTX	136 (23.0%)	104 (25.9%)	8 (7.8%)	24 (27.6%)	**0.0001**	0.7414	**0.0003**
MMF	99 (16.7%)	74 (18.4%)	16 (15.5%)	9 (10.3%)	0.4965	0.0693	0.2918
CYC	70 (11.8%)	50 (12.4%)	10 (9.7%)	10 (11.5%)	0.4450	0.8078	0.6895
CYA	23 (3.9%)	19 (4.7%)	2 (1.9%)	2 (2.3%)	–	–	–
CLQ and HCQ	11 (1.9%)	7 (1.7%)	0 (0.0%)	4 (4.6%)	–	0.1033	–
RTX	8 (1.4%)	6 (1.5%)	2 (1.9%)	0 (0.0%)	–	–	–
LEF	2 (0.3%)	2 (0.5%)	0 (0.0%)	0 (0.0%)	–	–	–
Other biological agents †	5 (0.8%)	3 (0.7%)	0 (0.0%)	2 (2.3%)	–	–	–
IVIG	9 (1.5%)	8 (2.0%)	1 (1.0%)	0 (0.0%)	–	–	–
No maintenance treatment	36 (6.1%)	28 (7.0%)	6 (5.8%)	2 (2.3%)	0.6804	–	–

† Belimumab, tralokinumab, infliximab.
8 patients (5 with GPA and 3 with MPA) died < 6 months after AAV diagnosis – they were excluded from analysis pertaining maintenance therapy.
Assumed statistical significance level of $\chi 2$ test (with Yates correction if needed) = 0.05, adjusted with Bonferroni correction if multiple comparisons performed = 0.017.
Statistically significant p-values are **bolded**.
Abbreviations: GCs = glucocorticoids; AZA = azathioprine; MTX = methotrexate; MMF = mycophenolate mofetil; CYC = cyclophosphamide; CYA = cyclosporine; CLQ = chloroquine; HCQ = hydroxychloroquine; RTX = rituximab; LEF = leflunomide; IVIG = intravenous immunoglobulins.

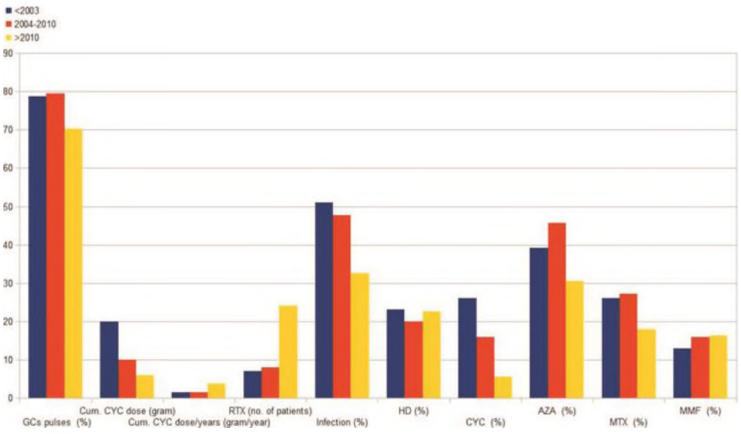

Fig. 1. Differences between chosen factors in AAV patients diagnosed in different periods.
Footnote: Cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil use during maintenance treatment
More detailed information is provided in the article text and in the Supplementary Table s5.
Abbreviations: GCs = glucocorticoids; CYC = cyclophosphamide; RTX = rituximab; AZA = azathioprine; MTX = methotrexate; MMF = mycophenolate mofetil; HD = haemodialysis.

Table 5
Association of chosen factors with infections occurrence.

	p	Odds ratio (exp B)	95% CI (lower border)	95% CI (upper border)
Cumulated CYC dose	0.092	1.012	0.998	1.026
GCs pulses use	**< 0.001**	2.759	1.677	4.536
Observation time	**0.029**	1.053	1.005	1.104
Haemodialysis	**0.018**	1.725	1.098	2.709

Binary logistic regression was used to obtain the results. Assumed level of statistical significance = 0.05.
Statistically significant p-values are **bolded**.
Abbreviations: CYC = cyclophosphamide; GCs = glucocorticoids.

4. Discussion

Based on the POLVAS registry database, we characterised the treatment of AAV in Poland. Demographic characteristics of described population did not vary considerably comparing to the populations in similar studies [11–15]. Generally, AAV therapy was consistent with recently published guidelines [16,17]. Of note, 6.1% of patients in our study did not receive any maintenance treatment, after exclusion of patients who had died before starting maintenance therapy. However, it might be a result of a short follow up in cases still being in an induction phase of remission by the time of recording their data in the registry. The median cumulative dose of cyclophosphamide amounted to 7.99 g, and does not exceed suggested whole-life dose of 25 g [17]. However, 9.33% of registered population received doses greater than 25 g. Cumulative doses of cyclophosphamide in our study were lower than those reported in patients before publication of CYCAZAREM [7] and CYCLOPS [18,19] results and comparable to or even lower than doses reported in later studies [11,20–23]. In the vast majority of cases GCs were used permanently during the whole observation time, probably due to predominance of cases with rather short observation time. Alternatively, it might show the tendency to prolong maintenance therapy with systemic GCs. Due to frequent adverse events associated with such treatment much shorter periods of steroid therapy are now suggested in the AAV patients [16,17,24].

There were some significant differences in the way AAV patients were treated depending on the clinical diagnosis. GCs were frequently the only agents used for induction of remission in EGPA patients, consistent with former guidelines to use steroid monotherapy in less severe cases [25,26]. However, according to newer data, concomitant use of GCs together with an additional immunosuppressive drug is suggested for all EGPA cases [27,28].More frequent use of methotrexate and azathioprine, less frequent use of cyclophosphamide as well as GCs pulses and no use of rituximab or plasmaphereses - these differences may reflect less severe course of EGPA, comparing to the other AAV entities. However, due to the lack of the Birmingham Vasculitis Activity Score (BVAS) and Five Factor Score (FFS) such assumption could not be definitely supported. Patients with MPA required haemodialysis significantly more frequently than GPA patients. This is consistent with other reports showing that diagnosis of MPA and anti-myeloperoxidase antibodies (anti-MPO) positivity are associated with severe renal involvement [29,30]. Cumulative dose of cyclophosphamide was higher in GPA comparing to MPA, which may be due to the higher tendency to relapse in anti-proteinase 3 antibodies (anti-PR3) positive cases [31,32]. However, it might be also influenced by shorter observational time in MPA group, as adjustment of cumulative dose of cyclophosphamide for the length of observation showed similar cumulative dose of cyclophosphamide per year of observation. We also noticed a relatively high number of MPA patients treated with GCs alone for induction remission (14.2%). As the trials in which such treatment regimen was administered showed unfavourable outcomes [33,34], and according to the current recommendations [16], such treatment should be abandoned.

Relatively less frequent use of rituximab in our AAV patients for induction of remission in severe disease exacerbation was mainly due to the lack of drug cost reimbursement program in our country at the time of data collection. Such refunding policy started by the end of 2016 which will allow for comparison between recently recommended remission induction regimens by cyclophosphamide or rituximab [16] in a prospective arm of the POLVAS study. We also found, that renal recovery after the time of temporary renal replacement therapy was associated with lower age. Moreover, the results for possible correlation of cyclophosphamide as well as plasmaphereses use with renal recovery - the factors reported to be associated with better renal outcomes by others - were near the threshold of statistical significance in our analysis [35–37]. Adverse events assumed to be related to the treatment were relatively common in the studied cohort.

Not surprisingly, the most frequently seen treatment side effects were infections (38.8% of all cases) - similarly to the other reports (range of infectious complications 26–39.9%) [11,15,38–40]. The factors associated with higher proportion of cases with infectious adverse events were time of observation, GCs pulses use and need for renal replacement therapy. The GCs pulses use might be the reflection of more intensive treatment and the higher total dose of GCs, which was associated with higher risk of infections in the other papers [15,41]. Three subgroups, differed by the time of diagnosis showed some interesting differences. Patients diagnosed in the earlier periods received

higher median cumulative doses of cyclophosphamide. Also, higher proportion of them developed infectious adverse events during follow up – an observation already made by the other authors [15]. The proportion of cases who developed infections was the lowest in the group with diagnosis of AAV established after 2010, comparing to the groups diagnosed in the earlier periods. It may be a reflection of changes in the maintenance therapy over time with replacement of cyclophosphamide by methotrexate, azathioprine or mycophenolate mofetil. On the contrary, it could also be associated with the shorter time of observation in this group. Interestingly, patients with diagnosis made after 2010 had significantly higher median dose of cyclophosphamide per year. It could be associated with the number of patients who were during or just after induction remission treatment in their first year of observation. A remarkable decrease in cyclophosphamide use as maintenance therapy was seen after CYCAZAREM, than RAVE and RITUXVAS [7–9] publications, which reflected the change in recommendations to rather use other agents than cyclophosphamide for this phase of treatment. Treatment-related factors associated with death were: need for haemodialysis which represents patients with severe renal involvement – the known factor of poor outcome in AVV [11,42], and steroid pulses use, which may indicate the group with more severe onset or further course of the disease. The cumulative number of relapses was associated with infection occurrence which could be a reflection of more intensive treatment, required during exacerbations of disease, which in turn may result in higher risk of infectious complications. The high prevalence of relapses in EGPA group was probably the result of assuming asthma exacerbations as relapses – such statement was made in another paper based on the data from the POLVAS population [7].

The main strength of our study is the number of cases included, which is the largest description of treatment strategies in AAV in Poland, and one of the largest ever reported.

On the contrary, there are also several drawbacks of this research. First of all, the data were collected retrospectively which may have led to some inconsistencies, errors and lacks of data. The significant shortage of data concerns especially the area of treatment related complications, which reaches about 50% of cases in some groups. Due to the difficulties in obtaining all necessary data, BVAS, Vasculitis Damage Index (VDI) and FFS indices were not assessed in the retrospective part of the database, so the objective judgment on cases severity is limited. Because of the retrospective character of data collection, the definitions of adverse events used in the registry are generally simplified, which may cause difficulties in detailed interpretation. Additionally, the number of adverse events and their severity was unknown. Relatively short time of observation may be considered as another limitation when analysing the cumulative dose of drugs used. The adjustment of the dose of immunosuppressant for a year of observation could partially overcome this limitation. The data from retrospective part of the database do not include also the information on the cumulative doses of GCs, which does not allow to analyse the overall steroid use. Furthermore, there are no data regarding the time to the occurrence of the analysed events, which makes it impossible to conduct the time-to-event analysis. Some adverse events of immunosuppression, such as neoplasms, may develop over longer period of time [43,44]. Therefore, their proportion might be underestimated in this study. Prospective cohort analysis may overcome aforementioned limitations in the future.

5. Conclusions

The treatment regimens and associated side effects among Polish AAV population described in retrospective branch of POLVAS registry seem to be similar to the other reports. Some differences in treatment between specific AAV entities were found – especially EGPA patients were treated less aggressively than those with MPA or GPA. Our analysis indicated the tendency to limit the cyclophosphamide in newer cases, especially in maintenance therapy. Lower rituximab administration was associated with no refunding policy to the end of 2016 year. The development of infections, which were the most frequent adverse effects of treatment, was related with GCs pulses use, time of observation and need for haemodialysis, but not with cumulative dose of cyclophosphamide.

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DATA statement

We claim that the submitted article is based on the data collected in the POLVAS Registry (Consortium of the Polish Vasculitis Registry) - Musial J, Wojcik K. Polish Vasculitis Registry: POLVAS. Pol Arch Intern Med. 2017; 127 (1):71-2.

Due to the extensive size of these data, we do not attach them to the manuscript.

We claim that we are authorized to use the data collected in the POLVAS databases by the POLVAS Steering Committee.

Declaration of competing interest

The authors declare no conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.advms.2020.01.002.

References

[1] Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. Revised international Chapel Hill Consensus conference nomenclature of vasculitides. Arthritis Rheum. 2012;65(1):1–11. 2013.
[2] Watts RA, Lane S, Scott DG. What is known about the epidemiology of the vasculitides? Best Pract. Res. Clin. Rheumatol. 2005;19(2):191–207.
[3] EUCERD Core Recommendations on Rare Disease Patient Registration and Data Collection. 5 June 2013.
[4] Padjas A, Sznajd J, Szczeklik W, Wojcik K, Wawrzycka K, Musial J. Rare disease registries: an initiative to establish vasculitis registry in Poland. Pol. Arch. Med. Wewn. 2014;124(3):143–4.
[5] Musial J, Wojcik K. Polish vasculitis registry: POLVAS. Pol. Arch. Intern. Med. 2017;127(1):71–2.
[6] Bloch DA, Michel BA, Hunder GG, McShane DJ, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Patients and methods. Arthritis Rheum. 1990;33(8):1068–73.

[7] Walsh M, Faurschou M, Berden A, Flossmann O, Bajema I, Hoglund P, et al. Long-term follow-up of cyclophosphamide compared with azathioprine for initial maintenance therapy in ANCA-associated vasculitis. Clin. J. Am. Soc. Nephrol. 2014;9(9):1571–6.
[8] Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N. Engl. J. Med. 2010;363(3):221–32.
[9] Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N. Engl. J. Med. 2010;363(3):211–20.
[10] Wojcik K, Wawrzycka-Adamczyk K, Wludarczyk A, Sznajd J, Zdrojewski Z, Masiak A, et al. Clinical characteristics of Polish patients with ANCA-associated vasculitides-retrospective analysis of POLVAS registry. Clin. Rheumatol. 2019 Sep;38(9):2553–63. https://doi.org/10.1007/s10067-019-04538-w. Epub 2019 Apr 23.
[11] Solans-Laque R, Fraile G, Rodriguez-Carballeira M, Caminal L, Castillo MJ, Martinez-Valle F, et al. Clinical characteristics and outcome of Spanish patients with ANCA-associated vasculitides: impact of the vasculitis type, ANCA specificity, and treatment on mortality and morbidity. Medicine (Baltim.) 2017;96(8):e6083.
[12] Guillevin L, Durand-Gasselin B, Cevallos R, Gayraud M, Lhote F, Callard P, et al. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. Arthritis Rheum. 1999;42(3):421–30.
[13] Comarmond C, Pagnoux C, Khellaf M, Cordier JF, Hamidou M, Viallard JF, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. Arthritis Rheum. 2013;65(1):270–81.
[14] Mohammad AJ, Jacobsson LT, Westman KW, Sturfelt G, Segelmark M. Incidence and survival rates in Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and polyarteritis nodosa. Rheumatology 2009;48(12):1560–5.
[15] Charlier C, Henegar C, Launay O, Pagnoux C, Berezne A, Bienvenu B, et al. Risk factors for major infections in Wegener granulomatosis: analysis of 113 patients. Ann. Rheum. Dis. 2009;68(5):658–63.
[16] Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann. Rheum. Dis. 2016;75(9):1583–94.
[17] Ntatsaki E, Carruthers D, Chakravarty K, D'Cruz D, Harper L, Jayne D, et al. BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. Rheumatology 2014;53(12):2306–9.
[18] Harper L, Morgan MD, Walsh M, Hoglund P, Westman K, Flossmann O, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. Ann. Rheum. Dis. 2012;71(6):955–60.
[19] de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al. Pulse versus daily oral cyclophosphamide for induction of remission in anti-neutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann. Intern. Med. 2009;150(10):670–80.
[20] Pagnoux C, Mahr A, Hamidou MA, Boffa JJ, Ruivard M, Ducroix JP, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N. Engl. J. Med. 2008;359(26):2790–803.
[21] JU Holle, Gross WL, Latza U, Nolle B, Ambrosch P, Heller M, et al. Improved outcome in 445 patients with Wegener's granulomatosis in a German vasculitis center over four decades. Arthritis Rheum. 2011;63(1):257–66.
[22] Koldingsnes W, Gran JT, Omdal R, Husby G. Wegener's granulomatosis: long-term follow-up of patients treated with pulse cyclophosphamide. Br. J. Rheumatol. 1998;37(6):659–64.
[23] Eriksson P, Jacobsson L, Lindell A, Nilsson JA, Skogh T. Improved outcome in Wegener's granulomatosis and microscopic polyangiitis? A retrospective analysis of 95 cases in two cohorts. J. Intern. Med. 2009;265(4):496–506.
[24] Pepper RJ, McAdoo SP, Moran SM, Kelly D, Scott J, Hamour S, et al. A novel glucocorticoid-free maintenance regimen for anti-neutrophil cytoplasm antibody-associated vasculitis. Rheumatology 2019;58(2):373.
[25] Mahr A, Moosig F, Neumann T, Szczeklik W, Taille C, Vaglio A, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): evolutions in classification, etiopathogenesis, assessment and management. Curr. Opin. Rheumatol. 2014;26(1):16–23.
[26] Szczeklik W, Jakiela B, Adamek D, Musial J. Cutting edge issues in the Churg-Strauss syndrome. Clin. Rev. Allergy Immunol. 2013;44(1):39–50.
[27] Miszalski-Jamka T, Szczeklik W, Sokolowska B, Karwat K, Miszalski-Jamka K, Jazwiec P, et al. Noncorticosteroid immunosuppression limits myocardial damage and contractile dysfunction in eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). J. Am. Coll. Cardiol. 2015;65(1):103–5.
[28] Sokolowska BM, Szczeklik WK, Wludarczyk AA, Kuczia PP, Jakiela BA, Gasior JA, et al. ANCA-positive and ANCA-negative phenotypes of eosinophilic granulomatosis with polyangiitis (EGPA): outcome and long-term follow-up of 50 patients from a single Polish center. Clin. Exp. Rheumatol. 2014;32(3 Suppl 82):S41–7.
[29] Moiseev S, Novikov P, Jayne D, Mukhin N. End-stage renal disease in ANCA-associated vasculitis. Nephrol. Dial. Transplant. 2017;32(2):248–53.
[30] Mohammad AJ, Segelmark M. A population-based study showing better renal prognosis for proteinase 3 antineutrophil cytoplasmic antibody (ANCA)-associated nephritis versus myeloperoxidase ANCA-associated nephritis. J. Rheumatol. 2014;41(7):1366–73.
[31] Walsh M, Flossmann O, Berden A, Westman K, Hoglund P, Stegeman C, et al. Risk factors for relapse of antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2012;64(2):542–8.
[32] Pagnoux C, Hogan SL, Chin H, Jennette JC, Falk RJ, Guillevin L, et al. Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis: comparison of two independent cohorts. Arthritis Rheum. 2008;58(9):2908–18.
[33] Ribi C, Cohen P, Pagnoux C, Mahr A, Arene JP, Puechal X, et al. Treatment of polyarteritis nodosa and microscopic polyangiitis without poor-prognosis factors: a prospective randomized study of one hundred twenty-four patients. Arthritis Rheum. 2010;62(4):1186–97.
[34] Hogan SL, Nachman PH, Wilkman AS, Jennette JC, Falk RJ. Prognostic markers in patients with antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. J. Am. Soc. Nephrol. 1996;7(1):23–32.
[35] Ma TT, Liu YR, Chen M, Zhao MH. Late restoration of renal function in patients with severe ANCA-associated glomerulonephritis who were dialysis-dependent at presentation. Clin. Rheumatol. 2018;37(8):2143–50.
[36] Lee T, Gasim A, Derebail VK, Chung Y, McGregor JG, Lionaki S, et al. Predictors of treatment outcomes in ANCA-associated vasculitis with severe kidney failure. Clin. J. Am. Soc. Nephrol. 2014;9(5):905–13.
[37] de Lind van Wijngaarden RA, Hauer HA, Wolterbeek R, Jayne DR, Gaskin G, Rasmussen N, et al. Chances of renal recovery for dialysis-dependent ANCA-associated glomerulonephritis. J. Am. Soc. Nephrol. 2007;18(7):2189–97.
[38] Yang L, Xie H, Liu Z, Chen Y, Wang J, Zhang H, et al. Risk factors for infectious complications of ANCA-associated vasculitis: a cohort study. BMC Nephrol. 2018;19(1):138.
[39] Wall N, Harper L. Complications of long-term therapy for ANCA-associated systemic vasculitis. Nat. Rev. Nephrol. 2012;8(9):523–32.
[40] Wong L, Harper L, Little MA. Getting the balance right: adverse events of therapy in anti-neutrophil cytoplasm antibody vasculitis. Nephrol. Dial. Transplant. 2015;30(Suppl 1):i164–70.
[41] Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. Rev. Infect. Dis. 1989;11(6):954–63.
[42] Flossmann O, Berden A, de Groot K, Hagen C, Harper L, Heijl C, et al. Long-term patient survival in ANCA-associated vasculitis. Ann. Rheum. Dis. 2011;70(3):488–94.
[43] Rahmattulla C, Berden AE, Wakker SC, Reinders ME, Hagen EC, Wolterbeek R, et al. Incidence of malignancies in patients with antineutrophil cytoplasmic antibody-associated vasculitis diagnosed between 1991 and 2013. Arthritis Rheum. 2015;67(12):3270–8.
[44] Shang W, Ning Y, Xu X, Li M, Guo S, Han M, et al. Incidence of cancer in ANCA-associated vasculitis: a meta-analysis of observational studies. PLoS One 2015;10(5):e0126016.

Supplementary Tables

Table s1. Disease serotypes (ANCA status based on indirect immunofluorescence and/or ELISA assay methods) and phenotypes (clinical syndromes)

ANCA status/Clinical syndrome		All	GPA	MPA	EGPA
Indirect immunofluorescence					
ANCA - any type		469 (88.3%†)	334 (94.9%)	102 (99.0%)	33 (43.4%)
c-ANCA		330 (62.1%)	310 (88.1%)	11 (10.7%)	9 (11.8%)
p-ANCA		129 (24.3%)	19 (5.4%)	92 (89.3%)	18(23.7%)
Atypical		10 (1.9%)	2 (0.6%)	4 (3.9%)	4 (5.3%)
Unknown type		7 (1.3%)	5 (1.4%)	0 (0.0%)	2 (2.6%)
Absent		62 (11.7%)	18 (5.1%)	1 (1.0%)	43 (56.6%)
Not tested/no data		94 (15.0%)	65 (15.6%)	3 (2.8%)	26 (25.5%)
ELISA assay					
Anti-PR3	**Positive**	344 (65.4%)	326 (85.8%)	12 (11.3%)	6 (12.0%)
	Negative	182 (34.6%)	54 (14.2%)	84 (87.5%)	44 (88.0%)
Anti-MPO	**Positive**	137 (26.9%)	28 (7.8%)	86 (85.1%)	23 (46.9%)
	Negative	373 (73.1%)	332 (92.2%)	15 (14.9%)	26 (53.1%)

† Percentages of cases with available data

Abbreviations: c-ANCA = cytoplasmic ANCA pattern; p-ANCA = perinuclear ANCA pattern; PR-3 = proteinase-3; MPO= myeloperoxidase

Table s2. Differences between cases hemodialyzed temporarily and permanently.

	Hemodialyzed temporarily	**Hemodialyzed permanently/ End stage renal disease**	**p-value**
Men	58.1 %	54.9 %	0.7280
Age (years) *	54	60	**0.0015**
GPA **	74.4 %	60.4 %	0.1134
Plasmaphereses	41.9 %	26.7 %	0.0779
GCs pulses use	75.7 %	81.5 %	0.4673
CYC use in induction therapy	92.9 %	80.2 %	0.0632

Assumed statistical significant level of $\chi 2$ test (with Yates correction if needed) = 0.05
*Analysis performed with Mann -Whitney U test (assumed level of significance=0.05). Median values of age are presented.
** Percent of GPA cases from total number (GPA and MPA cases).
Statistically significant p-values are **bolded**.

Abbreviations: CYC = cyclophosphamide; GCs = glucocorticoids

Table s3. Cumulative doses of cyclophosphamide and rituximab

		All	GPA	MPA	EGPA	p-value
Cumulative dose of CYC (gram)	**Median (quartiles)**	7.99 (4.18-14.0)	9.00 (5.3-16.0)	5.00 (2.0-8.0)	6.00 (5.4-8.58)	**<0.0001**
Cumulative dose of CYC/years of observation (gram/year)	**Median (quartiles)**	2.65 (1.21-5.14)	2.59 (1.22-5.14)	3.12 (1.20-6.27)	2.12 (0.89-3.24)	0.5023
Cumulative dose of RTX (milligram)	**Median (quartiles)**	2000.0 (1500-2800)	2000.0 (1500-2800)	2000.0 (700-2000)	0.00 (0)	0.3322*

Analysis performed with Kruskal-Wallis test (assumed level of significance=0.05) with post Hoc pairwise comparisons.
*Analysis performed with Mann -Whitney U test, regarding GPA and MPA cases (assumed level of significance=0.05).
Statistically significant p-values are **bolded**.

Abbreviations: CYC = cyclophosphamide; RTX = rituximab; GCs = glucocorticoids

Table s4. Characteristics of cases in which cumulative dose of cyclophosphamide exceeded 25.0 g

Number of all cases	46
Number of GPA cases	44
Number of MPA cases	2
Proportion of the whole group treated with cyclophosphamide	46/493; 9.33%
Maximum cumulative dose (g)	182
Median dose (g)	47
First quartile – Third quartile	36-76

Table s5. Differences between chosen factors in AAV patients diagnosed in different periods

Date of diagnosis	<2004 (I)	2004-2010 (II)	>2010 (III)	p (I vs II)	p (I vs III)	p (II vs III)
Number of patients	69	195	351	-	-	-
Patients treated with GCs pulses (at least one)	37/47; 78.72%;	116/146; 79.45%;	220/313; 70.29%;	0.9146	0.2328	0.0390
Median cumulative cyclophosphamide dose (gram)	20	10	6	**0.0020***	**<0.0001***	**<0.0001***
Median cumulative dose of cyclophosphamide/ years of observation (gram/year)	1.52	1.52	3.70	1.0000	**<0.0001***	**<0.0001****
Use of rituximab (no. of patients)	7	8	24	0.0656	0.3546	0.1866
Patients with infection	27/53; 50.94%	77/158; 47.73%	108/331; 32.63%	0.7807	**0.0006**	**0.0095**
Haemodialysis (permanently and temporarily)	15/65; 23.08%	38/190; 20.00%	79/349; 22.64%	0.5977	0.4782	0.9379
Cyclophosphamide use†	18/69; 26.09%	31/195; 15.90%	20//351; 5.70%	0.0614	**<0.0001**	**0.0001**
Azathioprine use†	27/69; 39.13%	89/195; 45.64%	107/351;30.48%	0.3490	0.1590	**0.0004**
Methotrexate use†	18/69; 26.09%	53/195; 27.18%	63/351; 17.95%	0.8604	0.1173	**0.0115**
Mycophenolate mofetil use†	9/69; 13.04%	31/195; 15.90%	57/351; 16.24%	0.5699	0.5049	0.9171

Analyses performed with Kruskal-Wallis test with post Hoc pairwise comparisons or $\chi 2$ test (with Yates correction if needed) and $\chi 2$ test. Assumed level of significance=0.05, (adjusted with Bonferroni correction if multiple comparisons performed = 0.017).

*Post hoc tests p-values. Kruskal Wallis test $p<0.0001$

**Post hoc tests p-values. Kruskal Wallis test $p<0.0001$

† In maintenance therapy

Statistically significant p-values are **bolded**.

Table s6. Treatment -associated adverse events

	All	GPA	MPA	EGPA	GPA/MPA p-value	GPA/ EGPA p-value	MPA/ EGPA p-value
Skin*	99/555 (17.8%)	83/398 (20.9%)	10/105 (9.5%)	6/52 (11.5%)	**0.0078**	0.1127	0.6945
Hematologic	53/554 (9.6%)	35/398 (8.8%)	15/104 (14.4%)	3/52 (5.8%)	0.0879	0.6365	0.1838
Infection	214/551 (38.8%)	151/398 (37.9%)	44/101 (43.6%)	19/52 (36.5%)	0.3008	0.8446	0.4029
Digestive system	78/549 (14.2%)	58/395 (14.7%)	10/104 (9.6%)	10/50 (20.0%)	0.1801	0.3249	0.0726
Autoimmune disorders	3/557 (0.5%)	1/399 (0.3%)	0/105 (0.0%)	2/53 (3.8%)	-	-	-
Neurologic system	43/559 (7.7%)	27/402 (6.7%)	10/105 (9.5%)	6/52 (11.5%)	0.3247	0.2076	0.6945
Neoplasms	9/552 (1.6%)	7/394 (1.8%)	2/105 (1.9%)	0/53 (0.0%)	-	-	-
Constitutional symptoms	145/549 (26.24%)	119/395 (30.1%)	15/102 (14.7%)	11/52 (21.2%)	**0.0018**	0.1805	0.3124

Assumed statistical significance level of $\chi 2$ test (with Yates correction if needed)= 0.05, adjusted with Bonferroni correction if multiple comparisons performed= 0.017.
Statistically significant p-values are **bolded**.

***Definitions of treatment-associated adverse events:**
Skin complications: Urticaria/Rash at the site of drug injection/Other rash
Hematologic: Leukopenia (<2500/ul)/Thrombocytopenia<100000/ul
Infection: Skin/Upper airways/Lower airways/Urinary system/Genital infection/Digestive tract/Central nervous system/Sepsis/Tuberculosis/Multifocal progressive leukoencephalopathy/Other infections
Digestive system: Liver (liver function tests > 3x ULN)/Stomach ache/Intestinal inflammation/Nausea and/or vomiting/Other
Autoimmune disorders: Lupus-like syndrome/Interstitial lung disease (based on HRCT image)/Other
Neurologic system: Demyelinating disorder/Neuropathy (mono or polyneuropathy)/Epileptic seizures/Headache/Spasticity/Other
Neoplasms: Lymphoma/Leukaemia/Non-melanoma skin cancer/Other
Constitutional/general symptoms: Fever/Flu-like symptoms/Vertigo/Fatigue/Mental disorders/Other

Abbreviations: ENT = ear, nose, throat

Respiratory involvement in antineutrophil cytoplasmic antibody-associated vasculitides: a retrospective study based on POLVAS registry

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Abstract

Objective

The study aimed to characterise the Polish population of (ANCA)-associated vasculitides (AAV) with respiratory involvement (RI), in comparison to the subgroup without lung manifestations and the other cohorts.

Methods

Retrospective analysis of the Polish population of AAV with RI was conducted, based on data from the POLVAS registry. Standard descriptive statistics, $\chi 2$ test, and Mann-Whitney U test were used to perform comparisons.

Results

Among 461 cases qualified to this study, there were 316 cases with RI (68.5%), 206 with granulomatosis with polyangiitis (GPA) (65.2%), 80 with eosinophilic granulomatosis with polyangiitis (EGPA) (25.3%) and 30 with microscopic polyangiitis (MPA) (9.5%). Proportion of RI in GPA, MPA, and EGPA accounted for 67.8%; 40.0%; 97.6%, respectively. The number of relapses was higher in the RI group (median 1.0 vs. 0.0; p=0.01). In the subgroup of combined GPA and MPA with RI, the trends toward higher proportion of deaths (11.7% vs. 5.7%; p=0.07), relapses requiring hospitalisation (52.2% vs. 42.4%, p=0.07) and relapses requiring admission to the intensive care unit (5.6% vs. 1.4%, p=0.09) were observed, median maximal concentration of CRP was higher (46 vs. 25 mg/l; p=0.01) and more aggressive treatment was administered.

Conclusion

Prevalence of RI in the Polish population of AAV is similar to the values reported in the literature, however, the proportion observed in GPA is closer to those presented in Asian than Western European cohorts. RI seems to be associated with a more severe course of disease and its presence prompts more aggressive treatment.

Key words

ANCA, vasculitis, AAV, respiratory involvement, lung involvement

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Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) is a group of rare (1), autoimmune diseases of unknown aetiology and varied clinical image, which may present as a systemic disease with multiorgan involvement. The group of AAV consists of three distinct entities: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) (2). The diagnostic process leading to establishing the diagnosis of AAV is complex. Usually, it requires a combination of clinical data, laboratory tests, imaging and histopathologic analysis of tissues from a biopsy.

Respiratory system involvement is one of the frequent manifestations, which in some cases is the most severe one, significantly influencing the outcome (3-5). Pulmonary manifestations in AAV are diverse and depend on the particular entity and ANCA pattern. The most common types of lung involvement in GPA are nodules with or without cavities, infiltrates and focal consolidations. In contrast, diffuse alveolar haemorrhage (DAH) and interstitial lung disease (ILD) are most typical in MPA. On the other hand, asthma is present in over 95% of EGPA cases, while ground-glass opacities in lung imaging are the second most prevalent respiratory manifestation (3-8). The Consortium of the Polish Vasculitis Registry (POLVAS) is a multicentre initiative designed to collect data, regarding prevalence, clinical features, treatment and outcomes of vasculitides among the Polish population. More detailed information on the POLVAS project is presented separately (9-12).

Being aware of the respiratory involvement significance in the course of AAV (8, 11, 13-16), we decided to detail the Polish population of AAV patients with respiratory involvement, based on data gathered in the POLVAS retrospective database.

Materials and methods

Six hundred and twenty-five cases of AAV diagnosed from 1990 to 2016 and remaining under the care of POLVAS affiliated centres were included in the retrospective part of the POLVAS database. The retrospective analysis was conducted and relevant data were collected using electronic questionnaires. All cases of AAV available in the documentation gathered in the POLVAS affiliated centres were included. Cases had to satisfy the American College of Rheumatology (ACR) classification criteria and/or the 2012 Revised International Chapel Hill Consensus criteria (2, 17).

Respiratory involvement in POLVAS database was defined as the occurrence of at least one symptom, sign, result of imaging test or condition attributable to AAV from the list included in POLVAS questionnaires. The list is presented in Table I. The status of respiratory involvement was unknown in 5 cases included in the POLVAS database, 620 cases were therefore qualified for further analysis. From the group encompassing the cases with respiratory involvement according to POLVAS definition, we selected only those with radiologically confirmed lesions. This subgroup was compared to the subgroup without respiratory involvement. The study was carried out under the ethical principles of The Declaration of Helsinki developed by the World Medical Association. The study protocol was approved by the Jagiellonian University Bioethics Committee (Krakow, Poland) No. 122/6120/25/2016. All POLVAS participating centres acquired local ethics committee approval.

Standard descriptive statistics were used. The normal distribution of variables was checked by the Shapiro-Wilk test. To compare the studied groups $\chi 2$ test (with Yates correction if needed) for dichotomous variables and Mann-Whitney U test for continuous variables were used. The p-value <0.05 was assumed as statistically significant, modified with Bonferroni correction when multiple comparisons were performed. Calculations were conducted with StatSoft Statistica 13 software (StatSoft®, Tulsa, OK, USA).

Results

Four hundred and seventy-five cases presented with respiratory involvement, according to POLVAS defini-

tion. From this group, 316 individuals (66.5%) had radiological confirmation of pulmonary abnormalities (RI group). They were included into further analysis and compared to the group without respiratory involvement (non-RI group), which involved 145 cases. After exclusion of the cases with pulmonary abnormalities but without proving on imaging tests, the prevalence of respiratory involvement in the selected group amounted to 68.5% (316/461).

Patients from the non-RI group were older than those form the RI group at the time of diagnosis (median values: 53 *vs.* 51 years). The prevalence of GPA, MPA and EGPA in the RI group amounted to 65.2%, 9.5% and 25.3%, respectively. Respiratory involvement with radiological confirmation was present in 97.6% *vs.* 67.8% *vs.* 40.0% cases of EGPA, GPA and MPA cases, respectively. The differences were statistically significant. The details regarding the comparison of particular AAV presence between RI and non-RI groups are included in Table II.

Most of the RI patients had additional organ involvement (97.8%). In both groups the most affected organs were kidneys (in the MPA subgroup 90.0% *vs.* 97.7% in the RI and non-RI groups, respectively), ear/nose/throat and musculoskeletal system. In the RI group constitutional symptoms, ear/nose/throat (ENT), cardiovascular, gastrointestinal, central and peripheral nervous systems involvement were present significantly more frequently than in the non-RI patients (89.8% *vs.* 80.6%, 74.3% *vs.* 60.0%, 23.5% *vs.* 9.0%; 16.6% *vs.* 7.6%; 10.6% *vs.* 4.1%; 28.8% *vs.* 15.9%, respectively).

There was no difference in mortality between the RI and non-RI groups, however raw proportion of deaths was higher in the RI group (9.0% *vs.* 5.8%). The overall number of relapses were significantly higher in the RI group (median=1 *vs.* median=0, respectively). The percentage of cases, requiring hospitalisation or admission to the intensive care unit (ICU) were also higher in the RI group, however they did not reach statistical significance. Patients from the non-RI group

Table I. Symptoms, signs, conditions and results of additional tests attributable to respiratory involvement included in the POLVAS questionnaire.

Symptoms and signs	Dyspnoea Dry cough Wet cough with purulent sputum Haemoptysis Wheezing Pleural pain Other symptoms/signs related to respiratory system
Results of imagining tests	Lung fibrosis Nodules or cavities in lungs Lung infiltration Diffuse alveolar haemorrhage Pleural effusion
Other clinical conditions associated with respiratory involvement	Respiratory disorders requiring oxygen therapy Respiratory failure requiring intubation

Table II. Comparison of chosen parameters between the RI and non- RI groups.

	RI group	Non-RI group	*p*-value
General data			
GPA	206/316; 65.2%	98/145; 67.6%	0.61
MPA	30/316; 9.5%	45/145; 31.0%	**<0.01**
EGPA	80/316; 25.3%	2/145; 1.4%	**<0.01**[*]
Men	149/316; 47.2%	57/145; 39.3%	**0.12**
Age at the time of diagnosis (years)	51.0 (36.0-60.0)	53.0 (40.0-65.0)	0.02
Time of observation (months)	57.0 (24.0-98.0)	41.0 (16.0-103.0)	0.13
Smoking (current or past)	74/207; 35.7%	38/97; 39.2%	0.56
Symptoms and signs			
Constitutional symptoms	283/315; 89.8%	116/144; 80.6%	**0.01**
Musculoskeletal system	185/310; 59.7%	78/145; 53.8%	0.24
Skin	121/314; 38.5%	46/143; 32.2%	0.19
Eye/ophthalmological manifestations	65/312; 20.8%	31/143; 21.7%	0.84
Ear/nose/throat (ENT)	234/315; 74.3%	87/145; 60.0%	**<0.01**
Cardiovascular system	74/315; 23.5%	13/144; 9.0%	**<0.01**
Gastrointestinal system	52/314; 16.6%	11/145; 7.6%	**0.01**
Kidneys	175/315; 55.6%	88/142; 62.0%	0.20
Genitourinary system	7/315; 2.2%	1/144; 0.7%	0.44[*]
Central nervous system (CNS)	33/312; 10.6%	6/145; 4.1%	**0.02**
Peripheral nervous system	218/306; 28.8%	23/145; 15.9%	**<0.01**
Deaths and relapses			
Deaths	28/310; 9.0%	8/137; 5.8%	0.25
Total number of relapses	1.0 (0.0-2.0)	0.0 (0.0-1.0)	**0.01**
Relapses requiring hospitalisation (at least one)	135/277; 48.7%	59/141; 41.8%	0.18
Relapses requiring ICU stay	14/276; 5.1%	2/140; 1.4%	0.12
Laboratory tests			
cANCA presence	170/268; 63.4%	72/121; 59.5%	0.46
pANCA presence	51/268; 19.0%	42/121; 34.7%	**<0.01**
ANCA absence	47/268; 17.5%	7/121; 5.8%	**<0.01**
anti-PR3	168/254; 66.1%	80/130; 61.5%	0.2553
anti-MPO	52/252; 20.6%	42/127; 33.1%	**0.01**
Eosinophilia	84/275; 30.5%	5/125; 4.0%	**<0.01**
Maximal CRP serum concentration (mg/l); [&]	38.0 (12.0-90.3)	25.1 (6.6-75.7)	0.06
Maximal creatinine concentration (mg/dl)	1.0 (1.0-2.1)	1.3 (1.0-4.6)	**0.02**

Data are presented as proportions and percentage or median and interquartile range, as appropriate. The proportions included in the columns described as RI group and non-RI group are the proportions of cases with the relevant feature to all cases with or without RI, respectively.
[*]Yates correction used; [&]at the time of diagnosis.
Statistically significant values are in bold.
PR3: proteinase 3; MPO: myeloperoxidase.

Table III. Comparison of treatment administered in the RI and the non-RI group.

	RI group	Non-RI group	*p*-value
Remission induction treatment			
GCs	310/315; 98.4%	131/144; 91.0%	**<0.01**
GCs without any other immunosuppressive drug	34/315; 10.8%	22/144; 15.3%	0.17
GCs pulses used (at least 1)	185/237; 78.1%	87/129; 67.4%	**0.03**
CYC	252/315; 80.0%	107/144; 74.3%	0.17
RTX	24/315; 7.6%	9/144; 6.3%	0.630
MTX	18/315; 5.7%	11/144; 7.6%	0.43
AZA	21/315; 6.7%	2/144; 1.4%	**0.03**
MMF	2/315; 0.6%	1/144; 0.7%	0.58*
IVIG	21/315; 6.7%	3/144; 2.1%	0.07
Plasmaphereses	29/313; 9.3%	11/139; 7.9%	0.64
Haemodialysis (permanently and temporarily)	48/312; 15.4%	37/140; 26.4%	**0.01**
Haemodialysis (permanently)	27/312; 8.7%	28/140; 20.0%	**<0.01**
Maintenance treatment			
GCs	223/265; 84.2%	115/139; 82.7%	0.71
AZA	118/265; 44.5%	42/139; 30.2%	**0.01**
MTX	73/265; 27.5%	35/139; 25.2%	0.61
MMF	48/265; 18.1%	19/139; 13.7%	0.25
CYC	32/265; 12.1%	11/139; 7.9%	0.20
CYA	15/265; 5.7%	5/139; 3.6%	0.36
RTX	3/265; 1.1%	2/139; 1.4%	0.83*

*Yates correction used. Statistically significant values are in bold.
CYC: cyclophosphamide; RTX: rituximab; MTX: methotrexate; AZA: azathioprine; MMF: mycophenolate; IVIG: intravenous immunoglobulins; CYA: cyclosporine.

had slightly higher maximal creatinine level.

Detailed information on the laboratory differences between the RI and non-RI groups are shown in Table II.

Interestingly, glucocorticosteroids (GCs) in the induction remission phase and GCs pulses were used significantly more frequently in the RI group (98.4% *vs.* 91.0% and 78.1% *vs.* 67.4%, respectively). Additionally, azathioprine was administered more frequently in the RI group in both remission induction and maintenance treatment (6.7% *vs.* 1.4% and 44.5% *vs.* 30.4%, respectively), comparing to the non-RI patients. On the other hand, patients from the non-RI group were haemodialysed more frequently than those from RI group. The details are presented in Table III.

We also analysed respiratory involvement in the subgroups – GPA, MPA and a combined subgroup of GPA and MPA individuals (GPA-MPA; EGPA cases excluded). In the latter subgroup, constitutional symptoms, musculoskeletal, ENT and CNS involvement were more prevalent in RI group, as compared to the non-RI group. Moreover, those subjects were characterised by a significantly elevated maximal CRP concentration (46 *vs.* 25 mg/l) and the more severe course of the disease, requiring relevantly more frequent use of GCs, GCs pulses, cyclophosphamide, and IVIG as well as rarer use of GCs as the only medicament during the remission induction treatment. The proportions of relapses requiring hospitalisation, relapses requiring ICU stay and deaths were also higher in the RI group, nonetheless did not reach statistical significance (52.2% *vs.* 42.4%, p= 0.07; 5.6% *vs.* 1.4%, p=0.09; 11.7% *vs.* 5.7%; p=0.07; respectively). On the other hand, permanent need for haemodialysis was observed more frequently in the non-RI group.

In the GPA subgroup the results were similar to these observed in the combined GPA-MPA subgroup, as the cases with GPA considerably prevailed in that cohort. Interestingly, all patients in MPA RI group were treated with GCs and cyclophosphamide during remission induction phase. In comparison to the MPA non-RI group, cyclophosphamide use as well as using GCs along with another immunosuppressive drug (not as an only medicament) during remission induction treatment were significantly more prevalent.

The details are presented in Table IV, only statistically significant differences are shown.

To better describe POLVAS cohort, we also performed analyses, considering all cases, meeting the POLVAS criteria of respiratory involvement (not only those with radiological confirmation). The data are included in the supplementary material.

Discussion

In the present study, in a large group of more than 450 cases, we have demonstrated that the prevalence of respiratory involvement in AAV is high (68.5%). Presence of pulmonary abnormalities was particularly widespread in our EGPA cohort (97.6%), as it usually reaches 90-91% (asthma excluded), according to the literature data (6, 7, 18). The percentage of respiratory involvement cases was higher in GPA than in MPA, which is commonly reported in other studies (7, 19, 20). The overall rate of respiratory involvement in GPA and MPA subgroups was comparable to the other cohorts. Of note, the proportion of cases with RI in GPA subgroup was more similar to those observed in Asian cohorts than in Western Europe (RI rates: GPA in Europe, range: 40.6%-67.0% *vs.* GPA in Asia, range: 67.6-69.5%) (14, 19-24). That may be the proper distinction between Central and Western European populations of GPA; however, it could also result from the differences in definitions or study protocols used in various studies (25).

Slight male predominance was noticed in the GPA and GPA-MPA RI subgroups with significant higher proportion of men, when compared to non-RI GPA and GPA-MPA subgroups. The data, regarding the sex ratio in the available literature are equivocal (4, 5, 8).

Pulmonary involvement was accompanied by other organ manifestations in the majority of cases. In particular, all individuals with MPA had at least one more organ affected, including kidneys in 90% of cases, similarly to the other reports (26). Cardiovascular, gastrointestinal, and peripheral nervous system involvement were observed more

Table IV. Differences between the RI and the non-RI group in defined subgroups.

	RI group		Non-RI group		*p*-value
GPA subgroup					
Men	106/206	51.5%	37/98	37.8%	0.03
Constitutional symptoms	186/205	90.7%	77/97	79.4%	0.01
Renal involvement	126/206	61.2%	45/96	46.9%	0.02
Maximal creatinine concentration (mg/dl); median	1.03	(1.0-2.78)	1.00	(0.88-2.2)	0.02
Maximal CRP concentration (mg/l); median[&]	45.5	(13.0-103.5)	22.0	(5.0-75.7)	0.02
Total GCs use[#]	200/205	97.6%	86/97	88.7%	<0.01
GCs without any other immunosuppressive drug[#]	7/205	3.4%	12/97	12.4%	<0.01
CYC use[#]	186/205	90.7%	74/97	76.3%	<0.01
GCs pulses use (at least one)	149/179	83.2%	57/86	66.3%	<0.01
MTX use[#]	9/205	4.4%	10/97	10.3%	<0.05
MPA subgroup					
GCs without any other immunosuppressive drug[#]	0/30	0.0%	10/45	22.2%	0.02*
CYC use[#]	30/30	100.0%	33/45	73.3%	0.01
GPA-MPA subgroup					
Men	123/236	52.1%	56/143	39.2%	0.01
MPA diagnosis	30/236	12.7%	45/143	31.5%	<0.01
Constitutional symptoms	212/235	90.2%	114/142	80.3%	0.01
Musculoskeletal system	150/233	64.4%	77/143	53.8%	0.04
Ear/nose/throat (ENT)	166/235	70.6%	87/143	60.8%	<0.05
Central nervous system involvement	27/232	11.6%	6/143	4.2%	0.01
Maximal CRP concentration (mg/l); median[&]	46.0	(14.0-105.0)	25.0	(6.6-75.1)	0.01
c ANCA presence	161/208	77.4%	72/119	60.5%	<0.01
p ANCA presence	38/208	18.3%	40/119	33.6%	<0.01
anti-PR3	164/218	75.2%	80/129	62.0%	0.01
anti-MPO	38/216	17.6%	41/126	32.5%	<0.01
Total GCs use[#]	230/235	97.9%	129/142	90.8%	<0.01
GCs without any other immunosuppressive drug[#]	8/235	3.4%	22/142	15.5%	<0.01
CYC use[#]	216/235	91.9%	107/142	75.4%	<0.01
IVIG use[#]	19/235	8.1%	3/142	2.1%	0.03
GCs pulses use (at least one)	175/208	84.1%	86/127	67.7%	<0.01
AZA use[$]	100/233	42.9%	42/137	30.7%	0.02
Haemodialysis (permanently)	27/232	11.6%	28/138	20.3%	0.02

*Yates correction used. [&]At the time of diagnosis. [#]In remission induction treatment. [$]In maintenance treatment.

frequently in the RI group, mainly due to EGPA prevalence, for which these manifestations are more characteristic than for the other AAV (6, 19). However, constitutional symptoms, ENT and CNS involvement prevailed both in the whole RI group and GPA-MPA subgroup. There was also a significant predominance of renal involvement in the GPA RI group, comparing to the GPA non-RI group, which might indicate the subset of more severe GPA presentation.

We found a higher rate of relapses in the all AAV RI group. However, the overall rate did not differ after the exclusion of EGPA cases, suggesting a milder course of EGPA exacerbations, which perhaps were usually asthma control worsening. Due to some specific features, like eosinophilic inflammation, association with asthma, and unique options for treatment, EGPA is considered to be a prominently different entity from the other AAV. Based on this knowledge we created and analysed the combined GPA-MPA subgroup, which approach is supported by literature data (27-29).

The analysis of GPA-MPA subgroup did not reveal the significant difference of death incidence, relapses requiring hospitalisation and relapses requiring ICU stay in the RI group, however there was a trend towards higher proportions of these parameters, comparing to the non-RI group Moreover, they reach statistical significance, when analysing all the cases fulfilling POLVAS definition of respiratory involvement (data shown in supplement). Additionally, CRP, which is one of the markers of active disease in AAV (30), was elevated (median maximal concentration) in the GPA-MPA RI group, comparing to the non-RI groups. Considerably more frequent use of GCs, GCs pulses, cyclophosphamide, IVIG and rarer administration of GCs without any other immunosuppressive drugs in the remission induction phase in GPA-MPA RI group (GCs and GCs pulses use also significantly more prevalent in all AAV RI group), comparing to non-RI group indicate more intense treatment regimen in cases with respiratory involvement. In MPA RI subgroup all cases were treated with GCs and cyclophosphamide, whereas some patients in the MPA non-RI group were administered only GCs for remission induction treatment. Together, these findings may suggest a more severe course of the disease and poorer outcome associated with respiratory involvement. Although respiratory involvement is not mentioned as the main factor influencing relapse rate or long-term outcome by recent reviews (1), particular manifestations, such as DAH or ILD with pulmonary fibrosis, are proved to be associated with poorer prognosis (4, 8, 15, 16, 31, 32). The occurrence of pulmonary damage is also a frequent reason for ICU admission or comorbidity of importance in patients treated in ICU, which suggests its association with more severe AAV exacerbation (33, 34). However, we did not obtain a statistically significant difference regarding mortality in the whole cohort as well as in the subgroups.

Nonetheless, taking into consideration that DAH might be the first manifestation of AAV with high mortality (13, 35, 36), as well as its high prevalence in AAV cases treated in the ICU units (32, 33), part of the most severe cases may be admitted to ICU wards and die without establishing a full diagnosis. It may result in the underestimation of deaths due to acute pulmonary manifestations in AAV.

On the other hand, we found higher median maximal creatinine concentration and more frequent need for haemodialysis in the all AAV non-RI subgroup. Permanent haemodialysis was also required more often in GPA-MPA non-RI

subgroup. Conversely, renal involvement and higher maximal creatinine concentration were observed in GPA RI subgroup. These findings seem to be associated with higher prevalence of MPA in non-RI groups, which is associated with frequent renal involvement and its severe course (19, 20, 26, 37).

Our study has several significant limitations. First of all, it is based on retrospective data, which may affect the possibility of forming precise conclusions and comparing results with prospective cohorts. Secondly, the definition of respiratory involvement used in the POLVAS database is broad; thus, its interpretation does not differentiate between distinct kinds of pulmonary manifestations. Therefore, it might not be possible to determine the type of respiratory involvement. It may lead to major misconceptions as the significance of asymptomatic pulmonary nodules and DAH is considerably different. To partially overcome this limitation, we selected the subgroup with radiologically confirmed disease. Unfortunately, there is no information on the type of performed imaging test, which may limit interpretation, as the sensitivity of X-ray and computed tomography is different. Due to the inclusion of only the cases with radiological confirmation, we had to exclude from the analysis 154 cases, which may result in the bias. Nevertheless, even after reducing the strength of the cohort, we were still able to involve over 450 cases in the study, which constitutes high number of AAV cases.

Therefore, we believe that number of cases included in the study, as well as the similarity of the main characteristics of this group to the other cohorts, makes this report reliable and valuable. Creation of the POLVAS registry by the collaboration of 9 prominent medical centres in Poland, which is to date the largest database of AAV cases in Poland, enabled to characterise Polish population of AAV. The ongoing prospective part of POLVAS project holds the promise of obtaining more detailed results.

The involvement of the respiratory system occurred in nearly 70% of the studied group. It was similar to the reports from the other countries, however, the proportion observed in GPA is closer to those presented in Asian than Western European cohorts. Respiratory involvement seemed to be associated with a more severe disease course in GPA and MPA and its presence prompted more aggressive treatment.

References

1. BERTI A, DEJACO C: Update on the epidemiology, risk factors, and outcomes of systemic vasculitides. *Best Pract Res Clin Rheumatol* 2018; 32: 271-94.
2. JENNETTE JC, FALK RJ, BACON PA *et al.*: 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; 65: 1-11.
3. THICKETT DR, RICHTER AG, NATHANI N, PERKINS GD, HARPER L: Pulmonary manifestations of anti-neutrophil cytoplasmic antibody (ANCA)-positive vasculitis. *Rheumatology* (Oxford) 2006; 45: 261-8.
4. HOMMA S, SUZUKI A, SATO K: Pulmonary involvement in ANCA-associated vasculitis from the view of the pulmonologist. *Clin Exp Nephrol* 2013; 17: 667-71.
5. MOHAMMAD AJ, MORTENSEN KH, BABAR J *et al.*: Pulmonary Involvement in Antineutrophil Cytoplasmic Antibodies (ANCA)-associated Vasculitis: The Influence of ANCA Subtype. *J Rheumatol* 2017; 44: 1458-67.
6. VAGLIO A, BUZIO C, ZWERINA J: Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): state of the art. *Allergy* 2013; 68: 261-73.
7. FRANKEL SK, SCHWARZ MI: The pulmonary vasculitides. *Am J Respir Crit Care Med* 2012; 186: 216-24.
8. ALBA MA, FLORES-SUAREZ LF, HENDERSON AG *et al.*: Interstitial lung disease in ANCA vasculitis. *Autoimmun Rev* 2017; 16: 722-9.
9. MUSIAL J, WOJCIK K: Polish Vasculitis Registry: POLVAS. *Pol Arch Intern Med* 2017; 127: 71-2.
10. PADJAS A, SZNAJD J, SZCZEKLIK W, WOJCIK K, WAWRZYCKA K, MUSIAL J: Rare disease registries: an initiative to establish vasculitis registry in Poland. *Pol Arch Med Wewn* 2014; 124: 143-4.
11. WOJCIK K, WAWRZYCKA-ADAMCZYK K, WLUDARCZYK A *et al.*: Clinical characteristics of Polish patients with ANCA-associated vasculitides-retrospective analysis of POLVAS registry. *Clin Rheumatol* 2019; 38: 2553-63.
12. BIEDRON G, WLUDARCZYK A, WAWRZYCKA-ADAMCZYK K *et al.*: Treatment and its side effects in ANCA-associated vasculitides - Study based on POLVAS registry data. *Adv Med Sci* 2020; 65: 156-62.
13. REINHOLD-KELLER E, BEUGE N, LATZA U *et al.*: An interdisciplinary approach to the care of patients with Wegener's granulomatosis: long-term outcome in 155 patients. *Arthritis Rheum* 2000; 43: 1021-32.
14. LAI QY, MA TT, LI ZY, CHANG DY, ZHAO MH, CHEN M: Predictors for mortality in patients with antineutrophil cytoplasmic autoantibody-associated vasculitis: a study of 398 Chinese patients. *J Rheumatol* 2014; 41: 1849-55.
15. SACOTO G, BOUKHLAL S, SPECKS U, FLORES-SUAREZ LF, CORNEC D: Lung involvement in ANCA-associated vasculitis. *Presse Med* 2020; 49: 104039.
16. SCHIRMER JH, WRIGHT MN, VONTHEIN R *et al.*: Clinical presentation and long-term outcome of 144 patients with microscopic polyangiitis in a monocentric German cohort. *Rheumatology* (Oxford) 2016; 55: 71-9.
17. BLOCH DA, MICHEL BA, HUNDER GG *et al.*: The American College of Rheumatology 1990 criteria for the classification of vasculitis. Patients and methods. *Arthritis Rheum* 1990; 33: 1068-73.
18. GIOFFREDI A, MARITATI F, OLIVA E, BUZIO C: Eosinophilic granulomatosis with polyangiitis: An overview. *Front Immunol* 2014; 5: 1-8.
19. LANE SE, WATTS RA, SHEPSTONE L, SCOTT DG: Primary systemic vasculitis: clinical features and mortality. *QJM* 2005; 98: 97-111.
20. SOLANS-LAQUE R, FRAILE G, RODRIGUEZ-CARBALLEIRA M *et al.*: Clinical characteristics and outcome of Spanish patients with ANCA-associated vasculitides: Impact of the vasculitis type, ANCA specificity, and treatment on mortality and morbidity. *Medicine* (Baltimore) 2017; 96: e6083.
21. GUILLEVIN L, DURAND-GASSELIN B, CEVALLOS R *et al.*: Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. *Arthritis Rheum* 1999; 42: 421-30.
22. SHARMA A, NAIDU G, RATHI M *et al.*: Clinical features and long-term outcomes of 105 granulomatosis with polyangiitis patients: A single center experience from north India. *Int J Rheum Dis* 2018; 21: 278-84.
23. FURUTA S, CHAUDHRY AN, ARIMURA Y *et al.*: Comparison of the Phenotype and Outcome of Granulomatosis with Polyangiitis Between UK and Japanese Cohorts. *J Rheumatol* 2017; 44: 216-22.
24. FURUTA S, CHAUDHRY AN, HAMANO Y *et al.*: Comparison of phenotype and outcome in microscopic polyangiitis between Europe and Japan. *J Rheumatol* 2014; 41: 325-33.
25. HOFFMAN GS, KERR GS, LEAVITT RY *et al.*: Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992; 116: 488-98.
26. VILLIGER PM AND GUILLEVIN L: Microscopic polyangiitis: Clinical presentation. *Autoimmun Rev* 2010; 9: 812-9.
27. VAN DER GEEST KSM, BROUWER E, SANDERS JS *et al.*: Towards precision medicine in ANCA-associated vasculitis. *Rheumatology* (Oxford) 2018; 57: 1332-9.
28. GROH M, PAGNOUX C, BALDINI C *et al.*: Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. *Eur J Intern Med* 2015; 26: 545-53.
29. WECHSLER ME, AKUTHOTA P, JAYNE D *et al.*: Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. *N Engl J Med* 2017; 376: 1921-32.
30. KRONBICHLER A, KERSCHBAUM J, GRUNDLINGER G, LEBERER J, MAYER G,

RUDNICKI M: Evaluation and validation of biomarkers in granulomatosis with polyangiitis and microscopic polyangiitis. *Nephrol Dial Transplant* 2016; 31: 930-6.

31. LAUQUE D, CADRANEL J, LAZOR R *et al.*: Microscopic polyangiitis with alveolar hemorrhage. A study of 29 cases and review of the literature. Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P). *Medicine* (Baltimore) 2000; 79(4): 222-33.
32. FLORES-SUAREZ LF, RUIZ N, SALDARRIAGA RIVERA LM, PENSADO I.: Reduced survival in microscopic polyangiitis patients with pulmonary fibrosis in a respiratory referral centre. *Clin Rheumatol* 2015; 34: 1653-4.
33. DEMISELLE J, AUCHABIE J, BELONCLE F *et al.*: Patients with ANCA-associated vasculitis admitted to the intensive care unit with acute vasculitis manifestations: a retrospective and comparative multicentric study. *Ann Intensive Care* 2017; 7: 39.
34. WLUDARCZYK A, POLOK K, GORKA J *et al.*: Patients with small-vessel vasculitides have the highest mortality among systemic autoimmune diseases patients treated in intensive care unit: A retrospective study with 5-year follow-up. *J Crit Care* 2018; 48: 166-71.
35. HOGAN SL, NACHMAN PH, WILKMAN AS, JENNETTE JC, FALK RJ: Prognostic markers in patients with antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. *J Am Soc Nephrol* 1996; 7: 23-32.
36. POLOK K, WLUDARCZYK A, SZCZEKLIK W: Clinical profile of patients with systemic autoimmune diseases treated in the intensive care unit who developed diffuse alveolar haemorrhage - an observational retrospective cohort study. *Anaesthesiol Intensive Ther* 2019; 51: 96-101.
37. FLOSSMANN O, BERDEN A, DE GROOT K *et al.*: Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis* 2011; 70: 488-94.

Supplementary Table S1. Comparison of chosen parameters between the RI and non- RI groups of all AAV, fulfilling POLVAS definition of respiratory involvement.

	RI group	Non- RI group	*p*-value
General data			
All AAV	475/620; 76.6%	145/620; 23.4%	
GPA	315/475; 66.3%	98/145; 67.6%	0.7765
MPA	60/475; 12.6%	45/145; 31.0%	**<0.0001**
EGPA	100/475; 21.1%	2/145; 1.4%	**<0.0001***
Men	238/475; 50.1%	57/145; 39.3%	**0.0227**
Age at the time of diagnosis (years)	49.8 ± 15.6	52.7 ± 16.3	0.0584
Symptoms and signs[a]			
Cardiovascular system	95/473; 20.1%	13/144; 9.0%	**0.0022**
Gastrointestinal system	72/473; 15.2%	11/145; 7.6%	**0.0183**
Central nervous system (CNS)	48/471; 10.2%	6/145; 4.1%	**0.0242**
Peripheral nervous system	119/464; 25.6%	23/145; 15.9%	**0.0150**
Deaths and relapses			
Deaths	48/465; 10.3%	8/137; 5.8%	0.1124
Total number of relapses	1.0 (0.0-2.0)	0.0 (0.0-1.0)	**0.0035**
Relapses requiring hospitalisation (at least one)	227/431; 52.7%	59/141; 41.8%	**0.0257**
Relapses requiring ICU stay	28/429; 6.5%	2/140; 1.4%	**0.0335**
Laboratory tests[a]			
p ANCA presence	86/399; 21.6%	42/121; 34.7%	**0.0033**
ANCA absence	54/399; 13.5%	7/121; 5.8%	**0.0203**
Eosinophilia	106/417; 25.4%	5/125; 4.0%	**<0.0001**
Maximal CRP serum concentration (mg/l); &	36.0 (11.0-90.0)	25.0 (6.0-75.0)	**0.0489**
Treatment#			
GCs in remission induction	455/473; 96.2%	131/144; 90.1%	**0.0120**
AZA in maintenance treatment	165/415; 39.8%	42/138; 30.4%	**0.0499**

The proportions included in the columns described as RI group and non-RI group are the proportions of cases with the relevant feature to all cases with or without RI, respectively.
Data are presented as median and interquartile range or mean and standard deviation, as appropriate.
[a]Yates correction used. &At the time of diagnosis #Only statistically significant values are presented.
PR3: proteinase 3; MPO: myeloperoxidase; GCs: glucocorticosteroids; AZA: azathioprine.

Supplementary Table S2. Differences between the RI and the non-RI group in defined subgroups of AAV, fulfilling POLVAS definition of respiratory involvement.

	RI group	Non-RI group	*p*-value
GPA subgroup			
Men	171/315; 54.3%	37/98; 37.8%	0.0043
Constitutional symptoms	276/314; 87.9%	77/97; 79.4%	0.0352
Renal involvement	206/315; 65.4%	45/96; 46.9%	0.0011
Relapses requiring ICU stay	17/305; 5.6%	0/94; 0.0%	0.0406*
Maximal creatinine concentration (mg/dl); median	1.2 (1.0-3.3)	1.0 (0.9-2.2)	0.0038
Maximal CRP concentration (mg/l); median [&]	40.0 (10.5-111.0)	22.0 (5.0-75.7)	0.0172
ANCA absence	10/270; 3.7%	7/75; 9.3%	0.0472
Total GCs use[#]	297/313; 94.9%	86/97; 88.7%	0.0307
GCs intravenous use[#]	249/313; 79.6%	60/97; 61.9%	0.0004
GCs without any other immunosuppressive drug[#]	18/313; 5.8%	12/97; 12.4%	0.0287
CYC use[#]	278/313; 88.8%	74/97; 76.3%	0.0020
Plasmaphereses	50/310; 16.1%	6/92; 6.5%	0.0194
GCs pulses use (at least one)	224/279; 80.3%	57/86; 66.3%	0.0070
MTX use[#]	12/313; 3.8%	10/97; 10.3%	0.0134
MTX use[$]	69/308; 22.4%	32/95; 33.7%	0.0265
MPA subgroup			
Relapses requiring hospitalisation	23/60; 38.3%	9/45; 20.0%	0.0434
anti-PR3 presence	3/53; 5.7%	9/42; 21.4%	0.0470*
CYC use[#]	54/60; 90.0%	33/45; 73.3%	0.0249
GPA-MPA subgroup			
Men	205/375; 54.7%	56/143; 39.2%	0.0016
MPA diagnosis	60/375; 16.0%	45/143; 31.5%	0.0001
Central nervous system involvement	40/371; 10.8%	6/143; 4.2%	0.0191
Deaths	47/365; 12.9%	8/135; 5.9%	0.0274
Relapses requiring hospitalisation	205/368; 55.7%	59/139; 42.4%	0.0077
Relapses requiring ICU stay	27/365; 7.4%	2/138; 1.4%	0.0193*
Maximal CRP concentration (mg/l); median [&]	43.0 (13.0-107.0)	25.0 (8.0-75.0)	0.0118
c ANCA presence	248/327; 75.8%	72/119; 60.5%	0.0015
p ANCA presence	70/327; 21.4%	40/119; 33.6%	0.0082
anti-PR3	256/342; 74.9%	80/129; 62.0%	0.0060
anti-MPO	272/331; 21.8%	41/126; 32.5%	0.0169
GCs intravenous use[#]	302/373; 81.0%	94/142; 66.2%	0.0004
CYC use[#]	332/373; 89.0%	107/142; 75.4%	0.0001
GCs without any other immunosuppressive drug[#]	24/373; 6.4%	22/142; 15.5%	0.0013
Plasmaphereses	61/370; 16.5%	11/137; 8.0%	0.0154
GCs pulses use (at least one)	270/334; 80.8%	86/127; 67.7%	0.0027

Only statistically significant values are presented.
*Yates correction used. [&]At the time of diagnosis. [#]In remission induction treatment. [$]In maintenance treatment.

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ANCA-associated vasculitis patients treated in Polish intensive care units – retrospective characteristics based on the POLVAS registry

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Abstract

Background: ANCA-associated vasculitides (AAV) is a group of rare disorders where inflammation and damage of the small blood vessels lead to dysfunction of the supplied organs. In severe flares of the disease patients may require intensive care unit (ICU) admission and treatment. The study aims to characterize Polish patients with AAV who were admitted to the ICU and compare them to the others.

Methods: An observational, retrospective study based on the POLVAS – registry of Polish adult patients with AAV was carried out. Patients admitted to the ICU (ICU group) were identified and compared with the patients who did not require ICU admission (non-ICU group). Characteristics and comparison between groups were made using standard statistic descriptive methods.

Results: 30 patients admitted to the ICU were identified among 573 cases included in the registry. All patients in the ICU group with available data were ANCA positive. The clinical manifestations related to the ICU admission were respiratory, renal and central nervous system involvement. The treatment regimen for remission induction was similar in both groups. Almost half of the patients in the ICU-group (48.3%) required dialysis, whereas in the non-ICU group it was 21.8% ($P = 0.01$). Infections were also more frequent in the ICU group (72.4% vs. 36.9% $P < 0.001$). The mortality rate among patients who needed ICU treatment was significantly higher when compared to the rest of the patients (53.6% vs. 7.8%; $P < 0.001$).

Conclusions: In the Polish AAV cohort one in twenty patients required ICU admission. This group was characterized by multiple organ involvement and high mortality.

Key words: autoimmune diseases, vasculitis, intensive care unit, ANCA, ICU, AAV.

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TABLE 1. Types of ANCA-associated vasculitides

Name	Abbreviation	Most frequent type of antibodies	
		Indirect immunofluorescence (IIF) test	ELISA test
Granulomatosis with polyangiitis	GPA	c-ANCA	Anti-PR3
Microscopic polyangiitis	MPA	p-ANCA	Anti-MPO
Eosinophilic granulomatosis with polyangiitis	eGPA	p-ANCA	Anti-MPO

ELISA – enzyme-linked immunosorbent assay, p-ANCA – perinuclear immunofluorescence ANCA pattern, c-ANCA – cytoplasmic immunofluorescence ANCA pattern, MPO – myeloperoxidase, PR-3 – proteinase 3

ANCA-associated vasculitides (AAV) is a group of three disorders in which inflammation and damage of the small blood vessels are correlated with the presence of antineutrophil cytoplasmic antibodies (ANCA). It is considered to be a rare disease with an incidence between 12 and 33 cases/1 million population/1 year [1].

The main clinical types of AAV, based on Chapel Hill classification [2], are granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (eGPA). Details are listed in Table 1.

In rare cases, AAV may be diagnosed based on clinical presentation and pathological findings without ANCA antibodies present [3]. The main pathomechanism consists of an immune-mediated inflammatory process that occurs in the walls of small vessels. Necrosis of these vessels leads to dysfunction of the supplied organs [3]. The clear causes of such an autoimmune reaction are still unknown. Clinical manifestation of the AAV can vary from single-organ involvement to rapidly progressing systemic disease. Almost every organ can be involved, although in the intensive care unit (ICU) setting the most important and potentially life-threatening manifestations are pulmonary, renal, and neurological [4].

Pulmonary involvement may lead to diffused alveolar haemorrhage with symptoms like cough, dyspnoea, and haemoptysis. Laboratory and imaging findings include decrease of haemoglobin concentration (Hb) in complete blood count (CBC), ground-glass opacities in chest X-ray and chest computed tomography (CT), blood-stained discharge in bronchoscopy, and hemosiderin loaded macrophages in broncho-alveolar lavage (BAL) [5, 6]. Other common respiratory tract manifestations are lung granulomas, bronchi mucosa ulcers, and tracheal or subglottic stenosis.

Renal involvement presents as glomerulonephritis with progressive (often rapidly) renal failure. Initially it can be asymptomatic. Typical laboratory findings are proteinuria, active urinary sediment with red blood cells and granular casts, and increased creatinine and urea serum concentration [7].

Neurological manifestation typically presents as mononeuritis multiplex. Much rarer, but potentially far more dangerous, is the central nervous system (CNS) involvement, which may lead to ischaemic or haemorrhagic stroke [8].

Diagnosis

The course of AAV is characterised by flares and remissions. In the case of a suspected flare of a disease, it is important to distinguish the disease from the complications of immunosuppressive treatment, like sepsis. Another ICU challenge is the diagnosis of the onset of the disease, which can be fulminant and life-threatening [9]. When pulmonary and renal disfunction coexist, so-called pulmonary-renal syndrome can be suspected and the diagnosis of vasculitis is very probable. Two main causes of pulmonary-renal syndrome are AAV and anti-glomerular basement membrane disease (Goodpasture syndrome – GPS) [10]. Immunological tests, such as ANCA screening, as well as rheumatology or clinical immunology consult, may allow a diagnosis to be made without delay. When possible, obtaining the samples for histopathological examination (e.g. kidney biopsy) may be extremely helpful to establish the diagnosis and severity of the disease, and hence to determine further procedures.

Treatment

Treatment of AAV is based on immunosuppression with glucocorticosteroids and additional immunosuppressants, such as cyclophosphamide or rituximab. It is carried out in two stages: intensive immunosuppressive treatment to induce disease remission, followed by milder maintenance therapy. In the ICU setting, in cases of AAV patients, induction therapy often requires an aggressive approach [11] and can be combined with interventions such as mechanical ventilation, continuous renal replacement therapy, and therapeutic plasma exchange [12]. There are also reports mentioning use of ECMO in diffused alveolar haemorrhage due to AAV [13, 14].

Patients with AAV admitted to an ICU can also suffer from severe infection and sepsis due to immunosuppressive treatment. Therefore, thorough

microbiological culture testing and broad-spectrum antibiotics when needed are essential.

POLVAS registry

The initiative named POLVAS is the Consortium of the Polish Vasculitis Registry, which was established to gather data on Polish adult vasculitis patients. A low incidence of AAV makes it impossible for a single centre to design and pursue clinical trials with a substantial number of patients; therefore, POLVAS was created by nine centres [15].

The presented research is based on the retrospective part of the POLVAS registry database. The main aim of the study is to characterise Polish patients with AAV who were admitted to the ICU and compare them to those who did not need such treatment.

METHODS

This is a multicentre, retrospective, observational, registry-based study on patients diagnosed with AAV between 1990 and 2016.

The study was carried out in accordance with the ethical principles of the Declaration of Helsinki developed by the World Medical Association. The study protocol was approved by the Jagiellonian University Bioethics Committee (Krakow, Poland) (approval no. 122/6120/25/2016). All POLVAS participating centres acquired Local Ethics Committee approval. Informed consent was obtained from the participants.

All included patients were diagnosed with vasculitis according to the American College of Rheumatology (ACR) classification criteria [16] and the 2012 Revised International Chapel Hill Consensus criteria [2]. Demographics, laboratory test results, clinical data, and treatment details were collected from the patients' medical records using an electronic form. The characteristics of the entire cohort are described in separate manuscripts [17, 18]. The presented analysis concerns comparison of the AAV patients admitted to the ICU (ICU group) to patients who did not require ICU admission (non-ICU group). ICU admission was defined in the form as "Severe disease flare requiring ICU admission".

Standard descriptive statistics were used. Normal distribution of variables was checked by the Shapiro-Wilk test, and homogeneity of variances was assessed by Levene's test. To compare the studied groups the χ^2 test (with Yates correction if needed) and Mann-Whitney *U* test were used. The *P*-value < 0.05 was considered as statistically significant, modified with Bonferroni correction when multiple comparisons were performed. The assumed level of significance for multiple comparisons according to Bonferroni correction equalled 0.017.

Calculations were performed with Statistica 13 software (StatSoft®, Tulsa, OK, USA).

RESULTS

Among 573 cases included in the retrospective POLVAS database, there were 30 cases (5.24%, 30/573; 18 males; $P = 0.21$) who were admitted to the ICU. Median time of observation (defined as the difference between the date of enrolment to the database and the date of the diagnosis) in the ICU group equalled three years (2.0–8.0), which was similar comparing to the non-ICU group (4 years, 2.0–8.0; $P = 0.98$). All patients in the ICU group were ANCA positive (in five cases there was no data regarding ANCA status), whereas 9% of cases in the non-ICU group were ANCA negative. MPA diagnosis, p-ANCA presence in IF test as well as anti-MPO presence in ELISA assay were associated with the risk of ICU admission ($P < 0.01$). The respiratory system was affected in 93.3% of ICU cases. Pulmonary, renal, CNS, and eye involvement were significantly more frequent in the ICU group ($P = 0.03$; $P = 0.01$; $P < 0.01$; $P = 0.03$). There were also more infections and more deaths in the ICU group compared to the non-ICU group (both $P < 0.01$). The details are presented in Table 2.

Initial treatment for remission induction was analysed. The main trends based on glucocorticosteroids and cyclophosphamide were the same in both groups; however, the cyclophosphamide cumulative dose was significantly higher in the non-ICU group, reaching 8.0 g (median: 4.7–15.0 g, $P < 0.01$). Therapeutic plasma exchange was used similarly in both groups, but intravenous immunoglobulins were more frequently given to the patients who needed ICU treatment during the course of disease (17.2% vs. 4.8%, $P < 0.01$). Almost half of the patients in the ICU-group (48.3%) required dialysis treatment at some point, whereas in the non-ICU group it was only 21.8% ($P = 0.01$). Details about the treatment are given in Table 3.

DISCUSSION

Generally, ANCA-associated vasculitides are diagnosed and treated in specialised internal medicine departments, like rheumatology, nephrology, or pulmonology. The majority of the patients do not require ICU admission. The data in the registry were gathered in the academic centres from across Poland, covering about 60% of the Polish population [17]. Our study shows that only 5.24% of all investigated AAV patients were admitted to an ICU. This is a relatively low number compared with other studies, in which 12–14% of AAV patients were treated in an ICU [19, 20]. This is probably due to the retrospective character of the presented part of the reg-

TABLE 2. The differences between the subgroup of cases who were admitted to the ICU and the subgroup of cases who were not treated in the ICU

Parameter	ICU group	Non-ICU group	*P*-value
Cases	30	543	–
Men	18/30, 60%	262, 48.3%	0.2101
Median observation (years)	3.0 (2.0–8.0)	4.0 (2.0–8.0)	0.9790
MPA	12/30, 40.4%	93/543, 17.1%	**MPA/GPA: 0.0047*** MPA/EGPA: 0.0371* GPA/EGPA: 0.4733*
GPA	17/30, 56.7%	385/543, 70.9%	
EGPA	1/30, 3.3%	65/543, 12.0%	
p-ANCA presence	13/25, 52.0 %	110/466, 23.6 %	**0.0014**
c-ANCA presence	12/25, 48.0%	310/466, 66.5%	0.0576
No ANCA	0/25, 0.0%	42/466, 9.0%	–
Anti-MPO presence	14/26, 53.8%	119/462, 25.8%	**0.018**
Anti-PR3 presence	13/26, 50.0%	321/477, 67.3%	0.0690
Cigarette smoking	5/16, 31.3%	143/375, 38.1%	0.5783
Infections	21/29, 72.4%	188/510, 36.9%	**0.0001**
Deaths	15/28, 53.6%	41/529, 7.8%	**< 0.0001**
Organ involvement			
Constitutional symptoms	24/30, 80.0%	455/540, 84.3%	0.5353
Musculo-skeletal system	21/30, 70.0%	307/538, 57.1%	0.1627
Skin	10/30, 33.3%	180/539, 33.4%	0.9944
ENT	16/30, 53.3%	354/543, 65.2%	0.1861
Eye	11/30, 36.7%	108/536, 20.1%	**0.0307**
Respiratory system	28/30, 93.3%	401/539, 74.4%	**0.0335**
Cardiovascular system	6/29, 20.7%	83/541, 15.3%	0.4396
Gastrointestinal system	7/30, 23.3%	63/541, 11.6%	0.0574
Renal	26/30, 86.7%	332/539, 61.6%	**0.0101**
CNS	7/30, 23.3%	42/539, 7.8%	**0.0031**
Peripheral neurological system	9/30, 30.0%	114/534, 21.3%	0.2642

Statistically significant *P*-values are shown in bold (assumed level of significance = 0.05)
* Assumed level of significance for multiple comparisons according to Bonferroni correction equals 0.017
ICU – intensive care unit, MPA – microscopic polyangiitis, GPA – granulomatosis with polyangiitis, EGPA – eosinophilic granulomatosis with polyangiitis, ANCA – antineutrophil cytoplasm antibodies, p-ANCA – perinuclear immunofluorescence ANCA pattern, c-ANCA – cytoplasmic immunofluorescence ANCA pattern, MPO – myeloperoxidase, PR-3 – proteinase 3

TABLE 3. Remission induction treatment modalities between ICU and non-ICU groups

Parameter	ICU group	Non-ICU group	*P*-value
GCs oral	15/29, 51.7%	338/543, 62.2%	0.2560
GCs iv	24/29, 82.8%	402/543, 74.0%	0.2101
CYC	27/29, (93.1%)	435/543, 80.1%	0.1368
RTX	4/29, 13.8%	40/543, 7.4 %	0.3640
TPE	6/29, 20.7%	65/535, 12.1%	0.1769
IVIG	5/29, 17.2%	26/543, 4.8%	0.0039
GS pulses*	24/29, 82.8%	347/475, 73.1%	0.2496
CTX cumulative dose in grams (median)	5.0 (2.0–8.0)	8.0 (4.7–15.0)	0.0084
RTX cumulative dose in grams (median)	2.4 (1.15–3.75)	2.0 (1.5–2.8)	0.7311
Dialysis	14/29, 48.3%	116/533, 21.8%	0.0010

Statistically significant *P*-values are bolded (assumed level of significance = 0.05)
* GS pulse was defined as at least one dose of ≥ 500 mg of methylprednisolone (or equivalent)
GCs – glucocorticoids, CYC – cyclophosphamide, RTX – rituximab, TPE – therapeutic plasma exchange, IVIG – intravenous immunoglobulins

istry with no follow-up. In addition, ICU admission criteria vary across countries [21, 22].

Knowledge of the main clinical manifestations can be valuable for the intensivists. Published studies show vasculitis as one of the most frequent autoimmune disease in the ICU [12, 23].

It is reported that AAV can have fulminant onset, and a significant number of diagnoses – reaching 10% – were first diagnosed in the ICU [9]. Unfortunately, in our study we lack data on whether the patients were diagnosed at the ICU. Moreover, information on whether it was the first or a subsequent flare that resulted in the ICU admission was also not included in the registry.

All patients with disease flares requiring ICU treatment presented multiorgan involvement. The most common manifestations in the ICU group were respiratory (93%) and renal (83%), which is consistent with other studies [9, 19, 20, 24]. Respiratory, re-

nal, and central nervous system manifestations were found more often in the ICU-group than in the non-ICU group. In the study by Demiselle *et al.*, patients with AAV treated in an ICU were compared to the control group treated in medical units; respiratory and CNS involvement were also more common in the ICU group, but not renal involvement [4]. It could be influenced by the fact that the control group was enrolled from the nephrology centres, where renal emergencies can be managed outside the ICU.

The treatment of the AAV has significantly changed over time. The last decade has brought a better understanding of immunosuppressive treatment with reduced doses of glucocorticosteroids and cyclophosphamide or new biological immunosuppressants, like rituximab. The registry's inclusion period is large; therefore, treatment differences may result from the state of the knowledge at the time as well as the availability of some methods. Our study shows that the general remission induction treatment regimen had no relation to the need for ICU treatment. However, a higher cumulative dose of cyclophosphamide in the non-ICU group could indicate that more aggressive immunosuppression can lead to better results, especially because the mortality was almost seven times higher in the ICU group, reaching 53.6%. Such high mortality may also be related to the fact that infections were twice as frequent as in the non-ICU group.

In another study by our team, we showed that patients with vasculitides have a worse prognosis than other autoimmune disease patients treated in the ICU [25].

AAV patients who needed ICU admission more often required intravenous immunoglobulins (IVIG). This may be due to the aforementioned registry's inclusion period, because 20 years ago IVIG therapy was more available than therapeutic plasma exchange. On the other hand, therapeutic plasma exchange frequency was comparable in both groups. Recently published results of the PEXIVAS trial by Walsh *et al.* showed that in ANCA-positive patients with renal exacerbation or alveolar haemorrhage, plasma exchange did not reduce end-stage kidney disease incidence or death [26].

Our study has several major limitations. It is based on retrospective data gathered in a registry and is focused on the overall medical characteristics of the cohort. We lack data on specialist ICU procedures and prognostic scales scores. Moreover, we were not able to establish from the registry's dataset any details of the ICU admissions. One of the biggest disadvantages of POLVAS registry is the scarcity of data on infectious complications. However, to our knowledge, it is the first attempt to estimate the problem of AAV in Polish ICUs. Hopefully the prospective part of the POLVAS registry will give more details on the matter.

CONCLUSIONS

In the Polish AAV cohort one in 20 patients required ICU admission. In this group respiratory, renal and central nervous system involvement was more often observed. The mortality was high. More prospective observational studies are needed to provide the full characteristics of AAV treated in ICUs in the Polish population.

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2. Presentation: none.

REFERENCES

1. Berti A, Dejaco C. Update on the epidemiology, risk factors, and outcomes of systemic vasculitides. Best Pract Res Clin Rheumatol 2018; 32: 271-294. doi: 10.1016/j.berh.2018.09.001.
2. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013; 65: 1-11. doi: 10.1002/art.37715.
3. Nakazawa D, Masuda S, Tomaru U, Ishizu A. Pathogenesis and therapeutic interventions for ANCA-associated vasculitis. Nat Rev Rheumatol 2019; 15: 91-101. doi: 10.1038/s41584-018-0145-y.
4. Demiselle J, Auchabie J, Beloncle F, et al. Patients with ANCA-associated vasculitis admitted to the intensive care unit with acute vasculitis manifestations: a retrospective and comparative multicentric study. Ann Intensive Care 2017; 7: 39. doi: 10.1186/s13613-017-0262-9.
5. Quartuccio L, Bond M, Isola M, et al. Alveolar haemorrhage in ANCA-associated vasculitis: Long-term outcome and mortality predictors. J Autoimmun. 2020; 108: 102397. doi: 10.1016/j.jaut.2019.102397.
6. Polok K, Wludarczyk A, Szczeklik W. Clinical profile of patients with systemic autoimmune diseases treated in the intensive care unit who developed diffuse alveolar haemorrhage - an observational retrospective cohort study. Anaesthesiol Intensive Ther 2019; 51: 96-101. doi: 10.5114/ait.2019.86164.
7. Binda V, Moroni G, Messa P. ANCA-associated vasculitis with renal involvement. J Nephrol 2018; 31: 197-208. doi: 10.1007/s40620-017-0412-z.
8. Wludarczyk A, Szczeklik W. Neurological manifestations in ANCA-associated vasculitis - assessment and treatment. Expert Rev Neurother 2016; 16: 861-863. doi: 10.1586/14737175.2016.1165095.
9. Monti S, Montecucco C, Pieropan S, Mojoli F, Braschi A, Caporali R. Life-threatening onset of systemic vasculitis requiring intensive care unit admission: a case series. Clin Exp Rheumatol 2015; 33 (2 Suppl): S-126-131.
10. Lee RW, D'Cruz DP. Pulmonary renal vasculitis syndromes. Autoimmun Rev 2010; 9: 657-660. doi: 10.1016/j.autrev.2010.05.012.
11. Kimmoun A, Baux E, Das V, et al. Outcomes of patients admitted to intensive care units for acute manifestation of small-vessel vasculitis: a multicenter, retrospective study. Crit Care 2016; 20: 27. doi: 10.1186/s13054-016-1189-5.
12. Heijnen T, Wilmer A, Blockmans D, Henckaerts L. Outcome of patients with systemic diseases admitted to the medical intensive care unit of a tertiary referral hospital: a single-centre retrospective study. Scand J Rheumatol 2016; 45: 146-150. doi: 10.3109/03009742.2015.1067329.
13. Kundu S, Sharma S, Minhas R, Scheers-Masters J, Saunders PC. Acute Respiratory Distress Syndrome Requiring Extracorporeal Membrane Oxygenation as the Initial Presentation of Anti-neutrophillic Cytoplasmic Auto-antibody Positive Vasculitis. Cureus 2019; 11: e6135. doi: 10.7759/cureus.6135.
14. Delvino P, Monti S, Balduzzi S, Belliato M, Montecucco C, Caporali R. The role of extra-corporeal membrane oxygenation (ECMO) in the treatment of diffuse alveolar haemorrhage secondary to ANCA-associated vasculitis: report of two cases and review of the literature. Rheumatol Int 2019; 39: 367-375. doi: 10.1007/s00296-018-4116-z.

15. Padjas A, Sznajd J, Szczeklik W, Wojcik K, Wawrzycka K, Musial J. Rare disease registries: an initiative to establish vasculitis registry in Poland. Pol Arch Med Wewn 2014; 124: 143-144.
16. Fries JF, Hunder GG, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Summary. Arthritis Rheum 1990; 33: 1135-1136.
17. Wojcik K, Wawrzycka-Adamczyk K, Wludarczyk A, et al. Clinical characteristics of Polish patients with ANCA-associated vasculitides-retrospective analysis of POLVAS registry. Clin Rheumatol 2019; 38: 2553-2563. doi: 10.1007/s10067-019-04538-w.
18. Biedron G, Wludarczyk A, Wawrzycka-Adamczyk K, et al. Treatment and its side effects in ANCA-associated vasculitides - Study based on POLVAS registry data. Adv Med Sci 2020; 65: 156-162. doi: 10.1016/j.advms.2020.01.002.
19. Cruz BA, Ramanoelina J, Mahr A, et al. Prognosis and outcome of 26 patients with systemic necrotizing vasculitis admitted to the intensive care unit. Rheumatology (Oxford) 2003; 42: 1183-1188. doi: 10.1093/rheumatology/keg322.
20. Frausova D, Brejnikova M, Hruskova Z, Rihova Z, Tesar V. Outcome of thirty patients with ANCA-associated renal vasculitis admitted to the intensive care unit. Ren Fail 2008; 30: 890-895. doi: 10.1080/08860220802353892.
21. Knapik P, Knapik M, Trejnowska E, et al. Should we admit more patients not requiring invasive ventilation to reduce excess mortality in Polish intensive care units? Data from the Silesian ICU Registry. Arch Med Sci 2019; 15: 1313-1320. doi: 10.5114/aoms.2019.84401.
22. Vincent JL, Marshall JC, Namendys-Silva SA, et al. Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. Lancet Respir Med 2014; 2: 380-386. doi: 10.1016/S2213-2600(14)70061-X.
23. Dumas G, Geri G, Montlahuc C, et al. Outcomes in critically ill patients with systemic rheumatic disease: a multicenter study. Chest 2015; 148: 927-935. doi: 10.1378/chest.14-3098.
24. Haviv Y, Shovman O, Bragazzi NL, et al. Patients With Vasculitides Admitted to the Intensive Care Unit: Implications From a Single-Center Retrospective Study. J Intensive Care Med 2017; 34: 828-834. doi: 10.1177/0885066617717223.
25. Wludarczyk A, Polok K, Gorka J, et al. Patients with small-vessel vasculitides have the highest mortality among systemic autoimmune diseases patients treated in intensive care unit: A retrospective study with 5-year follow-up. J Crit Care 2018; 48: 166-171. doi: 10.1016/j.jcrc.2018.08.037.
26. Walsh M, Merkel PA, Peh CA, et al. Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. N Engl J Med 2020; 382: 622-631. doi: 10.1056/NEJMoa1803537.

XII. OŚWIADCZENIA WSPÓŁAUTORÓW PUBLIKACJI

Kraków, 04 maja 2022r.

Dr Anna Władarczyk,
Zakład Intensywnej Terapii
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OŚWIADCZENIE

Jako współautor pracy: "**Treatment and its side effects in ANCA-associated vasculitides - study based on POLVAS registry data.**" (Advances in Medical Sciences 2020; Vol. 65 nr 1, s. 156-162) oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji polegał na: zaprojektowaniu badania, analizie statystycznej, interpretacji danych klinicznych, zgromadzeniu i analizie danych literaturowych oraz przygotowaniu i sprawdzeniu manuskryptu.

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Grzegorza Biedronia jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek. Grzegorza Biedronia polegający na: zaprojektowaniu badania, analizie statystycznej i interpretacji danych klinicznych, zgromadzeniu i analizie danych literaturowych oraz przygotowaniu i sprawdzeniu manuskryptu.

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Dr Krzysztof Wójcik,
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OŚWIADCZENIE

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Kraków, 04 maja 2022r.

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OŚWIADCZENIE

Jako współautor pracy: "**Respiratory involvement in ANCA-associated vasculitides - a retrospective study based on POLVAS registry.**" (Clinical and Experimental Rheumatology 2022 Apr 27; doi: 10.55563/clinexprheumatol/tvtyen. Online ahead of print.) oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji polegał na: zaprojektowaniu badania, zbieraniu danych klinicznych, analizie statystycznej, analizie i interpretacji danych klinicznych oraz przygotowaniu i sprawdzeniu manuskryptu.

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Kraków, 04 maja 2022r.

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(podpis współautora)

Kraków, 04 maja 2022r.

Prof. dr hab. Jacek Musiał,
II Katedra Chorób Wewnętrznych UJCM

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Zakład Alergii, Autoimmunizacji i Nadkrzepliwości
II Katedry Chorób Wewnętrznych
im. prof. Andrzeja Szczeklika UJ CM

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(podpis współautora)

Kraków, 04 maja 2022r.

Dr Anna Władarczyk,
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