Editorial

The targeted-biotherapy revolution for vasculitis treatment: major advances but certain concerns remain

L. Guillevin

Referral Center for Rare Autoimmune and Systemic Diseases, French Vasculitis Study Group, Hôpital Cochin, University of Paris, France.

Loïc Guillevin, MD

Please address correspondence to: Loïc Guillevin Referral Center for Rare Autoimmune and Systemic Diseases, French Vasculitis Study Group, Hôpital Cochin, University of Paris, 27 Rue du Faubourg Saint-Jacques, 75014 Paris, France. E-mail: loic.guillevin@orange.fr

Received on March 25, 2023; accepted on March 27, 2023.

Clin Exp Rheumatol 2023; 41: 780-783.

Key words: giant cell arteritis, tocilizumab, vasculitis, ANCA

Competing interests: none declared.

During the second part of the 20th century and the first part of the 21st, many things changed in the field of vasculitides: classification (1), description of pathogenic mechanisms (2, 3), description of genetic polymorphisms associated with some vasculitides (4, 5) and, as a consequence of these advances, new therapeutic strategies involving targeted therapies. Indications of these novel biotherapies have already been validated for giant-cell arteritis (GCA) (6, 7) and ANCA-associated vasculitides (AAVs) (8, 9). However, new treatments require thorough evaluation of their indications, careful analysis of the benefit/risk ratio and demonstration of that benefit on health expenses. Before considering those issues, I would like to summarise what was done during the past decades.

Vasculitides were lethal diseases and only a few patients recovered spontaneously in the pre-therapeutic era. The discovery that corticosteroids (CS) could treat those diseases achieved improvement for many patients, and one-third of those with polyarteritis nodosa (PAN) (10) and most with GCA recovered. The next step, at the end of the 1970s, was to give oral cyclophosphamide in combination with CS (11), for patients with necrotising vasculitides whose disease was not controlled by CS alone. Disease remission was obtained in 14/17 patients and cyclophosphamide was then largely prescribed for most necrotising vasculitides, especially Wegener's granulomatosis (now named granulomatosis with polyangiitis; GPA). The efficacy of first-line oral cyclophosphamide combined with CS was demonstrated prospectively against PAN in the 1980s (12). However, the dissemination of oral cyclophosphamide, not only for induction of remission but also for its maintenance, had a major impact on patient survival. Sterility, bladder cancer, leukaemias, other solid tumours ensued, sometimes 3 or 4 decades after completing therapy (13).

Since that time, oral cyclophosphamide use has been limited to remission induction (14) and other maintenance therapies were identified. Moreover, pulse cyclophosphamide progressively replaced oral administration (15), thereby limiting the risk of side effects by reducing the total dose received. The results of several prospective trials demonstrated the gain obtained with therapeutic strategies combining CS and cyclophosphamide, followed by azathioprine or methotrexate for maintenance, with at least 90% long-term survival (16-18).

Despite those bright and shiny survival and remission results, many concerns persisted. One of the most important was long-term CS toxicities. With remission obtained and along with the increasing longevity of the population, some issues have emerged, like the effects of osteoporosis, and renal or neurological sequelae on long-term survival (19, 20).

The new biologics have distinct mechanisms of action: rituximab depletes B cells thereby stopping antibody production, tocilizumab inhibits interleukin (IL)-6, mepolizumab IL5, dupilumab IL4 and IL13, and infliximab checks tumour necrosis factor (TNF). Another agent, like the C5a-inhibitor avacopan (21), aims at sparing CS and other immunosuppressants or biotherapies. Recourse to one of these new players in the field of vasculitis is not to satisfy clinicians' ambitions and egos in evaluating any novel therapeutic approaches. These drugs are available because they satisfy unmet needs. American, European and other countries' drug agencies have validated these drugs for thera-

peutic use, and governmental agencies and healthcare systems reimburse their costs, because they offer benefits for disease control, remission maintenance and safety. That last point necessitates thorough follow-up over the long-term because we do not yet have enough perspective to confirm that these new agents are safe and can replace conventional molecules.

Rituximab is certainly the biotherapy that has taken on a major place in the treatment of AAVs. It is not inferior to cyclophosphamide to induce remission (8, 22). Rituximab is now the treatment-of-choice for most patients, predominantly women of childbearing age and, more largely, all young patients, including children. Indications for cyclophosphamide adjunction to CS and/or rituximab are more limited and is often reserved for severely ill or old patients with glomerulonephritis and other anecdotical clinical situations.

Rituximab has also taken a predominant role in remission maintenance (9, 23), surpassing the conventional immunosuppressants, like azathioprine. Its effectiveness has been demonstrated but relapses can still occur (24). New rituximab infusions, administered systematically, on-demand (23) or based on clinical history (previous relapses) and perhaps even biological and/or immunological parameters (23), are also effective at preventing relapses. However, that agent induces B-cell depletion, which can persist for several months and facilitate severe infections. That explains why, despite the demonstration of long-term rituximab efficacy to prolong remission (25), we do not recommend treating patients for several years.

Notably, observations made during the COVID pandemic support that therapeutic choice (26-28), because immunocompromised patients died, including some with rituximab-treated AAVs. Those events should not condemn the indication of rituximab to induce remission, but its systematic long-term use should probably be limited to patients at risk of relapse. Prolonged administration should be now adapted to predictive relapse criteria, like previous relapses, ANCA persistence or reappearance and ANCA subtypes (22, 24).

Rituximab (29) also effectively induces remission of eosinophilic granulomatosis polyangiitis (EGPA), but is not inferior to the other strategies, like CS for patients with Five-Factor Score (FFS) = 0 (30) or cyclophosphamide for those with FFS ≥ 1 (31). Its appropriateness for maintenance is under evaluation.

The agent that is now taking on a large role in EGPA is mepolizumab. Indeed, when prescribed in adjunction to CS and immunosuppressants, it has been shown to be superior to placebo at preventing relapses (32). Another major interest of this anti-IL5 is that it facilitates CS-sparing and many anti-IL5-treated EGPA patients are now off CS. Studies are ongoing to assess the ability of mepolizumab to induce remission.

Dupilumab also has a place in EGPA treatment (33). This monoclonal antibody targeting IL4 and IL13 has other indications but has been shown to attenuate asthma and nasal polyps (33). Indeed, the outcomes of some case series favour the indication of dupilumab for patients whose disease is refractory to other treatments, including anti-IL5, or those with relapsing disease.

Infliximab, one of the first biologics, is usually not active against vasculitis, except for patients with adenosine deaminase 2 (ADA2) deficiency (34), a genetic form of PAN; this anti-TNF effectively prevents strokes, one of the most severe manifestations of the disease.

Tocilizumab, an anti-IL6 biotherapy, is now approved to treat GCA. In a randomised prospective trial comparing CS to CS + tocilizumab, tocilizumab-arm patients more frequently entered sustained CS-free remission than patients treated with CS alone (6, 7). Another randomised controlled trial comparing CS + methotrexate to tocilizumab + CS, is ongoing with the same objective of obtaining CS-sparing remission.

These new therapeutic strategies induced remission but with very little difference from conventional therapies, satisfying only non-inferiority criteria. In our opinion, their major advantage is CS-sparing, mainly for patients with GCA or EGPA. The negative long-term impact of CS is well-known. CS-associated long-term mortality and morbidities are mainly osteoporosis with fractures, diabetes, arterial hypertension and its consequences, and infections. Being able to lower the CS dose with biotherapies will change the patients' outcomes, especially for the elderly, and will improve their future survival and quality of life.

Recently, a C5a-receptor antagonist (21) was approved with the objective of tapering CS. Avacopan was non-inferior but not superior to simply tapering CS with respect to remission at week 26 and was superior to CS-tapering with respect to sustained remission at week 52. Serious adverse events were comparable in the two groups, as were vasculitis relapses. However, avacopan's real contribution could lie elsewhere, *i.e.* improving renal function of vasculitis patients with glomerulonephritis, but the encouraging results (21) must be supported by a prospective study. Considering CS-sparing, trial results (35) showed that it was possible to prescribe lower CS doses for rituximab-treated patients, with an induction dose of 0.5 mg/kg and discontinuation after 5 months vs 1 mg/kg and 10 mg, respectively, for the other group. Those findings, and others (36), clearly highlighted that patients have been overtreated with CS for decades and that tapering can be obtained, even without adjunction of new drugs.

The message from all those studies is that clinicians have taken into account the dimension of vasculitis evolution, which cannot be only viewed in the short term; clinicians must integrate long-term morbidities, and the deleterious effects of the disease and its treatments when therapies are prescribed at too high doses, for too long and sometimes inappropriately.

Targeted therapies are expensive. Health authorities are responsible not only for approving drugs but also for assessing their impact on each nation's healthcare budget. We advocate for the strong implication of clinicians, especially academics, to demonstrate that the benefits for patients should be associated with medical-economic studies. The National Institute for Health and Care of Excellence (NICE) which evaluates drugs for England and Wales,

investigates new drugs not only for their efficacy but also uses medical-economic criteria. In France and other European countries, determining the medical-economic impact of medications is now becoming crucial. Regarding maintenance therapies for AAVs, we proved that the rituximab was cost-effective with an Incremental Cost Effectiveness Ratio (ICER) of 224 euros to prevent one relapse (35). That determination has not been made for other biotherapies, leaving this responsibility to health authorities. In our opinion medical-economic studies should be an academic task, leading to wise, well-informed medical prescriptions.

The conclusions of this editorial are that, in the field of vasculitis, as well as many other medical specialties, the therapeutic advances are largely based on the availability of agents focusing on pathogenetic mechanisms. Inevitably, those molecules will progressively replace conventional drugs. We plead for their reasonable and wise use, which should be available worldwide and not only in countries with a high Gross National Product per capita. The second conclusion is that treatment objectives are not only to obtain and maintain remission "at all costs" but that clinicians should also protect patient's future, in terms of quality of life and limitation of morbidities. Sometimes, it could probably be more acceptable for a patient to experience a minor relapse, easily treated with minor drugs, than to systematically overtreat patients to prevent a severe relapse which might never occur. Hence, the future objective should be to establish criteria able to predict relapses and/or flares, and their severity, to target only patients at risk.

References

1. JENNETTE JC, FALK RJ, BACON PA *et al*.: 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; 65(1): 1-11. https://doi.org/10.1002/art.37715
2. VAN DER WOUDE FJ, RASMUSSEN N, LOBATTO S *et al*.: Autoantibodies against neutrophils and monocytes: tool for diagnosis and marker of disease activity in Wegener's granulomatosis. *Lancet* 1985; 1(8426): 425-9. https://doi.org/10.1016/s0140-6736(85)91147-x
3. XIAO H, HEERINGA P, HU P *et al*.: Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. *J Clin Invest* 2002; 110(7): 955-63. https://doi.org/10.1172/jci15918
4. LYONS PA, RAYNER TF, TRIVEDI S *et al*.: Genetically distinct subsets within ANCA-associated vasculitis. *N Engl J Med* 2012; 367(3): 214-23. https://doi.org/10.1056/nejmoa1108735
5. LYONS PA, PETERS JE, ALBERICI F *et al*.: Genome-wide association study of eosinophilic granulomatosis with polyangiitis reveals genomic loci stratified by ANCA status. *Nat Commun* 2019; 10(1): 5120. https://doi.org/10.1038/s41467-019-12515-9
6. VILLIGER PM, ADLER S, KUCHEN S *et al*.: Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet* 2016; 387(10031): 1921-7. https://doi.org/10.1016/s0140-6736(16)00560-2
7. STONE JH, TUCKWELL K, DIMONACO S *et al*.: Trial of tocilizumab in giant-cell arteritis. *N Engl J Med* 2017; 377(4): 317-28. https://doi.org/10.1056/nejmoa1613849
8. STONE JH, MERKEL PA, SPIERA R *et al*.: Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010; 363(3): 221-32. https://doi.org/10.1056/nejmoa0909905
9. GUILLEVIN L, PAGNOUX C, KARRAS A *et al*.: Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med* 2014; 371(19): 1771-80. https://doi.org/10.1056/nejmoa1404231
10. LEIB ES, RESTIVO C, PAULUS HE: Immunosuppressive and corticosteroid therapy of polyarteritis nodosa. *Am J Med* 1979; 67(6): 941-7. https://doi.org/10.1016/0002-9343(79)90634-x
11. FAUCI AS, KATZ P, HAYNES BF, WOLFF SM: Cyclophosphamide therapy of severe systemic necrotizing vasculitis. *N Engl J Med* 1979; 301(5): 235-8. https://doi.org/10.1056/nejm197908023010503
12. GUILLEVIN L, JARROUSSE B, LOK C *et al*.: Long-term follow-up after treatment of polyarteritis nodosa and Churg-Strauss angiitis with comparison of steroids, plasma exchange and cyclophosphamide to steroids and plasma exchange. A prospective randomized trial of 71 patients. The Cooperative Study Group for Polyarteritis Nodosa. *J Rheumatol* 1991;18(4): 567-74.
13. LE GUENNO G, MAHR A, PAGNOUX C *et al*.: Incidence and predictors of urotoxic adverse events in cyclophosphamide-treated patients with systemic necrotizing vasculitides. *Arthritis Rheum* 2011; 63(5): 1435-45. https://doi.org/10.1002/art.30296
14. JAYNE D, RASMUSSEN N, ANDRASSY K *et al*.: A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 2003; 349(1): 36-44. https://doi.org/10.1056/nejmoa020286
15. GUILLEVIN L, CORDIER JF, LHOTE F *et al*.: A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. *Arthritis Rheum* 1997; 40(12): 2187-98. https://doi.org/10.1002/art.1780401213
16. FLOSSMANN O, BERDEN A, DE GROOT K *et al*.: Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis* 2011; 70(3): 488-94. https://doi.org/10.1136/ard.2010.137778
17. SAMSON M, PUÉCHAL X, DEVILLIERS H *et al*.: Long-term follow-up of a randomized trial on 118 patients with polyarteritis nodosa or microscopic polyangiitis without poor-prognosis factors. *Autoimmun Rev* 2014; 13(2): 197-205. https://doi.org/10.1016/j.autrev.2013.10.001
18. SAMSON M, PUÉCHAL X, MOUTHON L *et al*.: Microscopic polyangiitis and non-HBV polyarteritis nodosa with poor-prognosis factors: 10-year results of the prospective CHUSPAN trial. *Clin Exp Rheumatol* 2017; 35 (Suppl. 103): 176-84.
19. LANGFORD CA: Management of systemic vasculitis. *Best Pract Res Clin Rheumatol* 2001; 15(2): 281-97. https://doi.org/10.1053/berh.2001.0144
20. PERRINEAU S, GHESQUIÈRE T, CHARLES P *et al*.: A French cohort of patients with giant cell arteritis: glucocorticoid treatment and its associated side effects. *Clin Exp Rheumatol* 2021; 39 (Suppl. 129): 155-60. https://doi.org/10.55563/clinexprheumatol/0nd4kk
21. JAYNE DRW, MERKEL PA, SCHALL TJ *et al*.: Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med* 2021; 384(7): 599-609. https://doi.org/10.1056/nejmoa2023386
22. SPECKS U, MERKEL PA, SEO P *et al*.: Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med* 2013; 369(5): 417-27. https://doi.org/10.1056/nejmoa1213277
23. CHARLES P, TERRIER B, PERRODEAU E *et al*.: Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). *Ann Rheum Dis* 2018; 77(8): 1143-9. https://doi.org/10.1136/annrheumdis-2017-212878
24. TERRIER B, PAGNOUX C, PERRODEAU E *et al*.: Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides. *Ann Rheum Dis* 2018; 77(8): 1150-6. https://doi.org/10.1136/annrheumdis-2017-212768
25. CHARLES P, PERRODEAU E, SAMSON M *et al*.: Long-term rituximab use to maintain remission of antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med* 2020; 173(3): 179-87. https://doi.org/10.7326/m19-3827
26. AVOUAC J, DRUMEZ E, HACHULLA E *et al*.: COVID-19 outcomes in patients with inflammatory rheumatic and musculoskeletal diseases treated with rituximab: a cohort study. *Lancet Rheumatol* 2021; 3(6): e419-e426. https://doi.org/10.1016/s2665-9913(21)00059-x
27. CONWAY R, GRIMSHAW AA, KONIG MF *et al*.: SARS-CoV-2 infection and COVID-19 outcomes in rheumatic diseases: a systematic literature review and meta-analysis. *Arthritis Rheumatol* 2022; 74(5): 766-75. https://doi.org/10.1002/art.42030

28. SATTUI SE, CONWAY R, PUTMAN MS *et al*.: Outcomes of COVID-19 in patients with primary systemic vasculitis or polymyalgia rheumatica from the COVID-19 Global Rheumatology Alliance physician registry: a retrospective cohort study. *Lancet Rheumatol* 2021; 3(12): e855-e864. https://doi.org/10.1016/s2665-9913(21)00316-7
29. TERRIER B, PUGNET G, DE MOREUIL C *et al*.: Rituximab versus conventional therapeutic strategy for remission induction in eosinophilic granulomatosis with polyangiitis: a double-blind, randomized, controlled trial [abstract]. *Arthritis Rheumatol* 2021; 73 (suppl. 9).
30. RIBI C, COHEN P, PAGNOUX C *et al*.: Treatment of Churg-Strauss syndrome without poor-prognosis factors: a multicenter, prospective, randomized, open-label study of seventy-two patients. *Arthritis Rheum* 2008; 58(2): 586-94. https://doi.org/10.1002/art.23198
31. COHEN P, PAGNOUX C, MAHR A *et al*.: Churg-Strauss syndrome with poor-prognosis factors: a prospective multicenter trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in forty-eight patients. *Arthritis Rheum* 2007; 57(4): 686-93. https://doi.org/10.1002/art.22679
32. WECHSLER ME, AKUTHOTA P, JAYNE D *et al*.: Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med* 2017; 376(20): 1921-32. https://doi.org/10.1056/nejmoa1702079
33. MOLINA B, URBAN ML, PADOAN R *et al*.: Safety and efficacy of dupilumab in patients with relapsing and/or refractory eosinophilic granulomatosis with polyangiitis [abstract]. *Arthritis Rheumatol* 2022; 74 (Suppl. 9).
34. OMBRELLO AK, QIN J, HOFFMANN PM *et al*.: Treatment strategies for deficiency of adenosine deaminase 2. *N Engl J Med* 2019; 380(16) 1582-4. https://doi.org/10.1056/nejmc1801927
35. FURUTA S NAKAGOMI D KOBAYASHI Y *et al*.: Effect of reduced-dose versus high-dose corticosteroids added to rituximab on remission induction in ANCA-associated vasculitis. *JAMA* 2021; 325(21): 2178-87. https://doi.org/10.1001/jama.2021.6615
36. WALSH M, MERKEL PA, PEH CA *et al*.: Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N Engl J Med* 2020; 382(7): 622-31. https://doi.org/10.1056/nejmoa1803537
37. MONTANTE A, LE BRAS A, PAGNOUX C *et al*.: Cost-effectiveness of rituximab versus azathioprine for maintenance treatment in antineutrophil cytoplasmic antibody-associated vasculitis. *Clin Exp Rheumatol* 2019; 37 (Suppl. 117): 137-43.