THERAPEUTIC ADVANCES in
Rare Disease

Review

The pharmacological treatment of granulomatosis with polyangiitis: a review of clinical trials registered in clinicaltrials.gov and the International Clinical Trials Registry Platform

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***Abstract*:** To date, there is no published overview of the drug pipeline in granulomatosis with polyangiitis (GPA), a rare disease. The aim of this study was to identify clinical trials from two study repositories. A review of clinical trials was conducted using publicly available data. Clinicaltrials.gov and International Clinical Trials Registry Platform were searched from inception until 25 September 2022. Only GPA-specific studies were included; these were described in detail. A total of 137 studies were identified in the trial repositories, of which 108 (79%) studies were found to concern GPA. Of these 108 studies, 67 enrolled GPA patients to investigate pharmacotherapy in this disease (62%). Most studies included all severity types ($n=51$; 76%); the scope of almost half of the studies was remission induction ($n=33$; 49%). The drug class which was by the most widely investigated in trials was the non-corticosteroid immunosuppressant drug class (46; 68.7%), monoclonal antibodies (32; 47.8%), and corticosteroids (31; 46.3%). There is a need for more GPA trials to generate evidence on effectiveness in terms of severity-specificity and maintenance of remission.

Plain language summary

The pharmacological treatment of granulomatosis with polyangiitis: a review of clinical trials

To date, there is no published overview of the drug pipeline in granulomatosis with polyangiitis (referred to in this paper as GPA), a rare disease. The aim of this study was to identify such studies from two study archives. Clinicaltrials.gov and International Clinical Trials Registry Platform (ICTRP) were searched from inception until 25th September 2022. Studies recruiting GPA patients were included; these were described in detail. A total of 137 studies were identified in the trial repositories, of which 108 were found to concern GPA. Of these 108 studies, 67 enrolled GPA patients to investigate the treatment of this disease through the administration of drugs. Most studies included all severity types ($n=51$); the scope of almost half of the studies was to induce remission ($n=33$). The drug classes which were the most widely investigated in trials were non-corticosteroid immunosuppressant drugs ($n=46$), monoclonal antibodies ($n=32$), and corticosteroids ($n=31$). There is a need for more GPA clinical trials to generate evidence on effectiveness of drugs in terms of severity-specificity and maintenance of remission.

Keywords: clinical trials, granulomatosis with polyangiitis, pharmacotherapy

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Introduction

Granulomatosis with polyangiitis (GPA) is a rare disease belonging to the anti-neutrophil cytoplasmic antibody (ANCA)-associated family of vasculitides. It has a yearly incidence ranging from 1 in 84,000 to 475,000 persons[1] and a global prevalence ranging between 20 and 150 cases per million.[2] Although the age of symptom onset varies significantly, GPA most commonly first presents among persons in their early 40s until their late 60s; onset of symptoms in children and young adults is much less common.[3–7] GPA appears to be more common among Caucasian populations rather than African or Asian populations.[8–10] The initial clinical presentation of GPA includes upper respiratory tract symptoms, such as epistaxis and sinusitis; the trachea and bronchi, as well as lung tissue, may also be involved.[11] After the onset of respiratory tract symptoms, the clinical presentation of GPA becomes more overtly vasculitis-related. Patients may develop a very wide range of symptoms, including arthralgia, neuritis, and cutaneous vasculitis.[11] The majority of GPA patients (60–80%) go on to develop renal symptoms due to necrotizing glomerulonephritis.[1] GPA is clinically categorized into severe or non-severe.

The pharmacological management of GPA is initially aimed at inducing disease remission, and once this is achieved, at maintaining remission. The main drugs used to manage GPA are cyclophosphamide, glucocorticoids, rituximab, methotrexate, mycophenolate mofetil, and azathioprine.[12] Since GPA is a rare disease, most drugs used to treat it are used off-label[13] with the exception of rituximab, which was approved in 2011 for the treatment of severe GPA.[14] The use of this particular drug expanded with an FDA-licensed indication for GPA in combination with glucocorticoids in 2011[15] and in children aged 2 and older in 2019.[16] Other drugs may be undergoing trials either as repurposed agents or as completely new experimental drugs. The most robust drug efficacy data are obtained from randomized clinical trials, but such studies may not be possible to conduct within a rare disease population due to a lack of cases as well as controls.[17] As a result, the need for drug efficacy data in rare diseases is usually greater than for other diseases. To date, there is no study that provides an overview of the clinical trials targeting the management of GPA. The aim of this study was therefore to address this research gap by identifying such studies from clinicaltrials.gov and the International Clinical Trials Registry Platform (ICTRP).

Methods

Study retrieval

Two databases were used to access the studies for this review: Clinicaltrials.gov and the ICTRP. ICTRP is maintained by the World Health Organization, whereas clinicaltrials.gov is a public repository of all studies that have received US government funding as well as some studies funded by commercial entities and unfunded studies. The ICTRP registry contains information on the study design, conduct, and administration of clinical trials carried out around the world. Deposited studies may include both interventional as well as observational studies.

The registries were searched from inception until 25 September 2022 for keywords 'granulomatosis with polyangiitis' and 'Wegener's granulomatosis'. Studies recruiting a GPA population and investigating the pharmacological treatment of GPA were included, even if the study did not enroll exclusively GPA populations. Studies that used vaccines were not considered to have used a drug; for example, a trial that investigated antibody response to vaccination (NTR1130) was excluded. Studies from both clinialtrials.gov and the ICTRP registry may be registered in more than one repository. Where trials in the ICTRP registry were registered in another database with more complete information, for example, the full study protocol was available in EU RCT registry, the repository with more information was used as a reference.

Data collection and coding

For each study, data was collected on study status (i.e., recruiting, terminated, suspended, completed, active not recruiting, not yet recruiting, unknown status, or withdrawn), whether results were available, which population was included (i.e., whether the population recruited comprised only GPA patients or otherwise) and whether the study was observational or interventional (i.e., a clinical trial). For clinical trials, detailed information on masking (i.e., none, open-label, double masking, triple masking, quadruple masking, not applicable, or unknown), treatment allocation (i.e., randomized or non-randomized) and interventional model (i.e.,

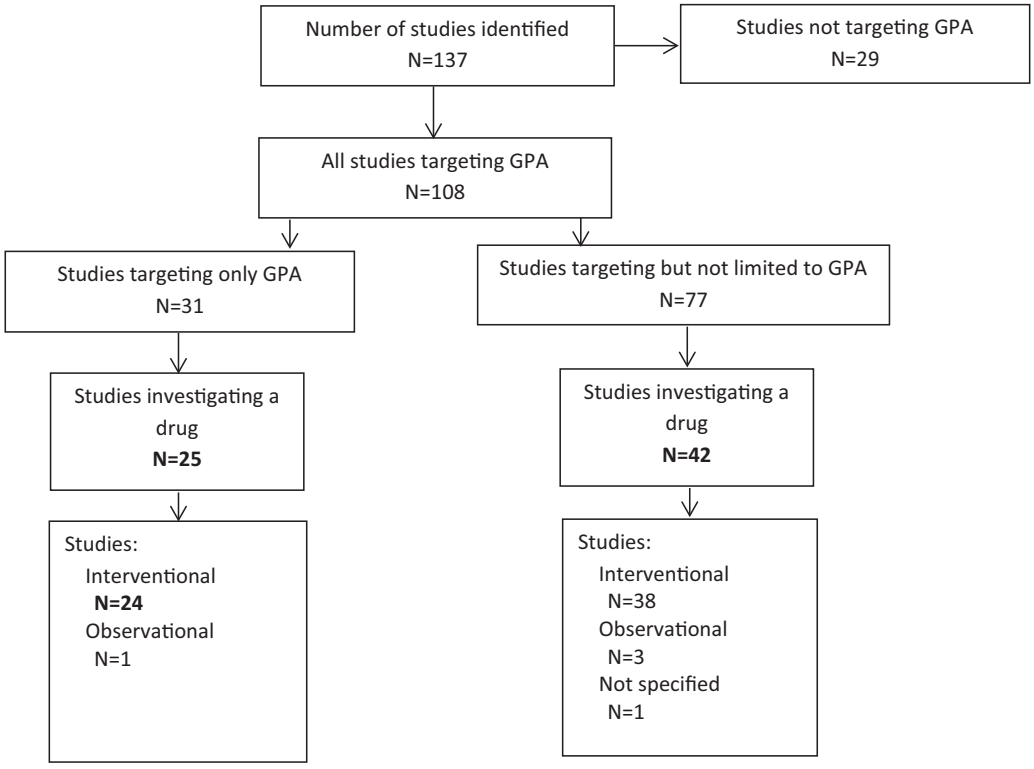

Figure 1. Flowchart of study selection.
GPA, granulomatosis with polyangiitis.

single group assignment, parallel assignment, other, not applicable, or unknown) was collected. For all studies, the purpose (i.e., treatment or other purpose) and study phase (phases I–IV) was recorded. In order to describe the extent of international collaboration, study stakeholders were identified and if they came from different countries, this was considered an instance of international collaboration. Each study drug investigated in a study was recorded, whether only one or more than one study was used. In addition, each drug was grouped according to its pharmacological class, in order to allow class-level descriptive analysis to be carried out. The drug classes were as follows: immunosuppressants, corticosteroids, monoclonal antibodies (MABs), selective T-cell costimulation blocker, BAFF-anatagonists, tumor necrosis factor (TNF) alpha inhibitors, anti-lymphocyte immunoglobulins, antibiotics, and hematopoietic agents.

Where possible, we screened the available study protocol to distinguish whether severe or non-severe GPA patients were recruited. Where a study did not specify the severity, it was assumed that all severity types were included. Information was also collected on whether the studies focused on remission induction or remission maintenance. Where studies enrolled patients with new or relapsing GPA and the aim of the study was not specified, it was assumed that the aim was remission induction. For multi-site studies, only one record per study was included. If at least one study had results, the whole multi-site study was considered to have results.

Data analysis

Descriptive analyses were used to present results. Data analysis was conducted using STATA.

Results

Clinicaltrials.gov and ICTRP registry

A total of 137 studies were identified in the trial repositories, of which 108 (79%) were found to concern GPA (Figure 1). Of these 108 studies, 67 enrolled GPA patients to investigate pharmacotherapy in this disease (62%). Just over half the studies (52%) included in this review

Table 1. General overview of all studies that include GPA and that investigate a medicinal product as identified from clinicaltrials.gov and ICTRP registry.

Study characteristics	Studies which focus on GPA alone *N* = 25	Studies which include but do not focus on GPA *N* = 42	Studies which include GPA *N* = 67
Status			
Recruiting	3 (12.0%)	5 (11.9%)	8 (11.9%)
Terminated	2 (8.0%)	3 (7.1%)	5 (7.5%)
Suspended	–	–	–
Completed	12 (48.0%)	23 (54.8%)	35 (52.2%)
Active not recruiting	2 (8.0%)	3 (7.1%)	5 (7.5%)
Not yet recruiting	1 (4.0%)	3 (7.1%)	4 (6.0%)
Unknown status/not specified	5 (20.0%)	4 (9.5%)	9 (13.4%)
Withdrawn	–	1 (2.4%)	1 (1.5%)
Study results			
No results available	20 (80.0%)	28 (66.7%)	48 (71.6%)
Has results	5 (20.0%)	14 (33.3%)	19 (28.4%)

GPA, granulomatosis with polyangiitis; ICTRP, International Clinical Trials Registry Platform.

were completed (Table 1). Only 12% of studies were recruiting and smaller proportions were active but not recruiting or not yet recruiting. There were 13% of studies whose status was unknown. Almost two-thirds of included trials did not have study results available ($n = 48$; 72%). Most studies identified were interventional ($n = 62$; 93%) with only four studies (6%) being classified as observational (Table 2). Overall, 34% of studies were phase II, 24% were phase III, and 18% were phase IV. Only 6% of studies were phase I.

Most studies included all severity types ($n = 51$; 76%), whereas much fewer studies included mild disease only ($n = 5$; 8%) or severe disease only (n = 8; 12; Table 3). The scope of almost half of the studies was remission induction ($n = 33$; 49%), followed by remission maintenance ($n = 18$; 27%). Five studies focused on both (8%). Just over half of studies were conducted with parallel assignment of treatment ($n = 38$; 57%). Almost a third of studies were open label ($n = 40$; 60%). The median size of the enrolled populations in the trials was 60 patients (25th–75th percentile: 27.5–140). The characteristics of the 67 studies identified are reported in full in Supplemental Appendix Table 1.

The drug class which was by the most widely investigated in trials was the non-steroidal immunosuppressant drug class, with just over a third of all studies focusing on GPA alone including at least one such drug ($n = 7$; 36.8%; Table 4). This was followed by corticosteroids ($n = 4$; 21%) and monoclonal antibodies ($n = 4$; 21%). The monoclonal antibodies investigated were rituximab ($n = 3$; 16%) and daclizumab ($n = 1$; 5%). Although non-corticosteroid immunosuppressant drugs were most frequently used as a class, each drug in this class was investigated in a maximum of seven studies; however, among individual drugs, prednisolone was the most commonly investigated drug, having been investigated in four (21%) studies. This was followed by rituximab, cyclophosphamide, and mycophenolate mofetil, which were each investigated by three studies.

The one observational study that was identified had incomplete information on study design and intervention (NCT00001473). This study, which

Table 2. Methodological overview of all studies that include GPA and that investigate a medicinal product as identified from clinicaltrials.gov and ICTRP registry.

Study characteristics	Studies which focus on GPA alone *N* = 25	Studies which include but do not focus on GPA *N* = 42	Studies which include GPA *N* = 67
General method			
Observational	1 (4.0%)	3 (7.1%)	4 (6.0%)
Interventional	24 (96.0%)	38 (90.5%)	62 (92.5%)
Not specified	–	1 (2.4%)	1 (1.5%)
Phase			
Phase I	3 (12.0%)	1 (2.4%)	4 (6.0%)
Phase II	10 (40.0%)	13 (31.0%)	23 (34.3%)
Phase III	6 (24.0%)	10 (23.8%)	16 (23.9%)
Phase IV	2 (8.0%)	10 (23.8%)	12 (17.9%)
Phases I and II	2 (8.0%)	–	2 (3.0%)
Phases II and III	1 (4.0%)	4 (9.5%)	5 (7.5%)
Not reported or unclassifiable	1 (4.0%)	4 (9.5%)	5 (7.5%)

GPA, granulomatosis with polyangiitis; ICTRP, International Clinical Trials Registry Platform.

was completed, aimed to investigate the efficacy and safety of prednisone and cyclophosphamide, followed by methotrexate. This study enrolled 100 patients.

Discussion

To our knowledge, the present study is the first to systematically review the pharmacological pipeline of GPA and provide an updated overview of clinical trials. Out of 24 studies targeting GPA alone, the majority ($N = 20$; 83.3%) investigated a drug. The remaining studies focused on the natural history of GPA (NCT03182049), optimizing disease monitoring through biomarkers (NCT01862068), identification of novel biomarkers (NCT01167491) and investigation of tissue abnormalities. GPA can be life- or organ-threatening, with patients developing symptoms such as alveolar bleeding, glomerulonephritis, cerebral vasculitis, mononeuritis multiplex, mesenteric ischemia, and limb/digit ischemia. However, as treatment for this disease improves life expectancy, unmet clinical needs emerge related to how to manage GPA in the long-term, including when the disease is in remission. The role of observational studies could potentially come into play here, in evaluating drug effectiveness over long observation periods. One such study was recently conducted by the French Vasculitis Study Group, which evaluated sustained remission of GPA after discontinuing therapy.[18] Similar observational studies are of great value as discontinuation of therapy is a likely possibility after remission, but very little is known about this aspect of GPA treatment.

Another interesting finding was that the study populations investigated in trials were very small, with a median of 60 patients (25th–75th percentile: 28–140). Small sample sizes are known to be common in rare disease trials due to difficulty in recruiting patients.[17] However, the problem of small population sizes is compounded by the fact that there is a large heterogeneity in the clinical types of GPA under study. This heterogeneity includes a range of severity investigated in a single trial, which means that it is difficult to extrapolate the evidence to clinical practice. Indeed, the most recent guidelines of the American College of

Table 3. Disease severity and scope of treatment among the studies identified from clinicaltrials.gov and ICTRP registry.

Study characteristics	*N* (%)
Severity	
All severity types	51 (76.1)
Mild disease only	5 (7.5)
Moderate to severe disease	1 (1.5)
Moderately severe disease only	1 (1.5)
Severity requiring rituximab only	1 (1.5)
Severe disease only	8 (11.9)
Scope of treatment	
Remission maintenance	18 (26.9)
Remission induction	33 (49.3)
Remission and induction	5 (7.5)
Other	6 (9.0)
Not specified or unclear	5 (7.5)
Interventional model	
Parallel assignment	38 (56.7)
Crossover assignment	1 (1.5)
Factorial assignment	3 (4.5)
Single group assignment	10 (14.9)
Not specified	15 (22.4)
Masking	
None	40 (59.7)
Single	3 (4.5)
Double	9 (13.4)
Triple	5 (7.5)
Quadruple	3 (4.5)
Not specified	7 (10.4)

ICTRP, International Clinical Trials Registry Platform.

Rheumatology/Vasculitis Foundation Guideline for the pharmacological management of GPA bases its recommendations primarily on severity.[19] Previous guidelines have also primarily classified patients and subsequent treatment based on severity.[12]

The drug class which was by far the most widely investigated in trials was the non-corticosteroid immunosuppressant drug class, monoclonal antibodies, and corticosteroids. Non-corticosteroid immunosuppressants and corticosteroids have likely been so commonly investigated because they are older drugs. On the other hand, monoclonal antibodies like rituximab are among the second most commonly used class of drugs in clinical trials. The long-term safety of rituximab in GPA has been shown in an international phase IV study, and although the incidence rate of severe infections was as high as 7.11 (95% CI: 4.55–10.58) per 100 patient-years,[20] the safety profile of this drug is considered favorable. Studying drug efficacy and safety in rare disease patients presents unique methodological challenges, such as identifying a sufficiently large sample size, ensuring the correct diagnosis of the disease, difficulty in finding comparators, ethical issues concerning the nature of the comparator and so on. In the last 10 years, pharmaceutical companies have increased their investment in rare disease drugs, including orphan drugs, as high-profit drugs, despite the small number of eligible patients. The development of drugs for common indications, such as hypertension and diabetes, has led to the availability of several drug classes that are widely used and are considered to have a good effectiveness-safety profile; it is difficult for drug development in this area to significantly target clinical needs better than they are already being targeted. In contrast, drugs used for rare diseases address a clinical need which is either truly unmet or poorly met. This includes both orphan drugs as well as the many drugs used off-label in rare diseases. In the case of GPA, practically all drugs used, except for rituximab and avacopan are used off-label. This highlights the importance of generating robust evidence not only to support the best use of these drugs in the future but also to describe how such drugs are being currently used.

A key theme in GPA therapeutics is drug repurposing, also known as drug repositioning, which is highlighted by the fact that many drugs studied in the clinical trials identified are off-label drugs. Repurposing involves the use of drugs which are already on the market for an indication which is not currently included in the marketing authorization.[21] This has the advantage of leveraging a

Table 4. Overview of drug use for trials including GPA populations – including only studies that consider a drug. Each drug and drug class was not mutually exclusive.

Single drug	*N* = 67 (%)	Drug class	*N* = 67 (%)
Cyclophosphamide	14 (20.9)	Immunosuppressant	46 (68.7)
Mycophenolate	8 (11.9)		
Methotrexate	7 (10.5)		
Gusperimus	4 (6.0)		
Azathioprine	12 (17.9)		
Cyclosporine	1 (1.5)		
Prednisolone	18 (26.9)	Corticosteroid	31 (46.3)
Methylprednisolone	6 (9.0)		
Corticosteroid NOS	7 (10.5)		
Daclizumab	1 (1.5)	MAB	32 (47.8)
Mepolizumab	1 (1.5)		
Belimumab	2 (3.0)		
Alemtuzumab	2 (3.0)		
Rituximab	19 (28.4)		
Infliximab	2 (3.0)		
Vilobelimab	3 (4.5)		
Obinutuzumab	1 (1.5)		
Efalizumab	1 (1.5)		
Abatacept	4 (6.0)	Selective T-cell costimulation blocker	22 (32.8)
Etanercept	2 (3.0)	TNF alpha inhibitor	
Trimethoprim/Sulfamethoxazole	1 (1.5)	Antibiotic	
Blisibimod	1 (1.5)	Other	
Anti-thymocyte globulin	1 (1.5)		
Filgrastim	1 (1.5)		
Tofacitinib	1 (1.5)		
Tocilizumab	3 (4.5)		
Avacopan	1 (1.5)		
Brensocatib	1 (1.5)		
Vitamin D	2 (3.0)		
Hydroxychloroquine	1 (1.5)		
Interleukin-10	1 (1.5)		
Interleukin-2	1 (1.5)		
Alendronate	1 (1.5)		

GPA, granulomatosis with polyangiitis; MAB, monoclonal antibody; NOS, not otherwise specified; TNF, tumor necrosis factor.

large body of pre-clinical and safety data already collected to obtain the marketing authorization, with the result that such data does not need to be collected again. This is very cost-effective for pharmaceutical companies and also gives them a head start in identify drug candidates which are safe enough to go directly to trial. Drug repurposing has been used in relatively common diseases such as Alzheimer's disease, where finding viable therapeutic agents is very challenging, but it has also been used in rare diseases, such as corneal dystrophy.[22] The role of repurposing emerges from the present study as the majority of drugs which have been included in trials were off-label drugs. The main limitation for GPA, as well as many other rare diseases, is that the pathophysiology is not fully understood, making it difficult to find therapeutic targets for drugs to reach.

Whether for repurposed drugs or otherwise, transparency is an importance element of evidence in rare disease therapeutics, that is, the data sources, methods underlying the studies, and funders must be clearly reported. One could argue that this is particularly important for rare diseases, as decisions on whether to approve a drug's marketing authorization may be taken based on a very small number of studies. However, this study showed that only 71.6% of trials including a GPA population had published results on the data repository. A study published in 2013 showed that 13.4% of studies registered between 2008 and 2012 reported results within 1 year of the trial being finalized.[23] A study published more recently found that only 41% of studies in clinicaltrials.gov did so within 2 years of completion, suggesting that while transparency may have improved, overall it is still not adequate.[24] Future research on GPA should aim to be more transparent in order to allow the scientific community understand it, critique it and build on it.

This study has strengths as well as limitations. Its strength is its novelty in identifying studies that investigate the pharmacological treatment of GPA and describing them in detail. This has not been done to date. However, the focus of the present review concerned trials that are registered in the two study repositories used, precluding the identification of relevant trials that were not registered. Nevertheless, it is very likely that all key trials are registered in either of the two repositories used. In fact, the methodology and data sources used made it possible for pivotal trials that included both GPA and other populations to be identified, including one trial that has led to the approval of avacopan for GPA and microscopic polyangiitis.[25] Like all reviews of publicly held repositories, the present study depends heavily on the quality of the data reported. It has been shown that the quality of data in clinicaltrials.gov is not consistently high, despite regulations issued by the Food and Drug Administration to promote this.[26] It has also been shown that data reporting in clinicaltrials.gov varies by type of study and type of funder.[27] This limitation cannot be addressed. However, we argue that similar repositories remain the best choice for an overview of clinical research being conducted or concluded around the world. The present study is limited to the description of studies which are clinical trials. As a result, it does not represent information obtained from real-world studies such observational post-marketing studies. Rare disease registries and drug registries in particular hold great potential to monitor the drug safety, and potentially also effectiveness, over long observation periods.[28] Ideally, findings from a clinical trial setting should be complemented by findings from such real-world settings.

Conclusion

There is a very limited number of clinical trials focusing on GPA treatment and many of these trials include GPA of all severity types, although clinical guidance is specific to severity type. There is also a lacuna concerning the treatment of GPA in remission and on drug discontinuation. These gaps can potentially be addressed with more carefully planned trials and complemented by observational studies, either using administrative data/electronic medical records or patient registries.

Declarations

Ethics approval and consent to participate

Not applicable since this study did not use primary data, sensitive data or data that was not publicly available.

Consent for publication

Not applicable.

Author contributions

Janet Sultana: Conceptualization; Data curation; Investigation; Methodology; Project administration; Writing – original draft.

Nikita Camilleri: Data curation; Formal analysis.

Salvatore Crisafulli: Methodology; Writing – review & editing.

John Joseph Borg: Methodology; Resources; Writing – review & editing.

Silvan Spagnol: Data curation; Methodology; Writing – review & editing.

Silvia Tillati: Data curation; Formal analysis; Methodology; Writing – review & editing.

Joseph Borg: Formal analysis; Writing – original draft; Writing – review & editing.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
The data which was used in the study is publicly available from the respective websites.

Supplemental material
Supplemental material for this article is available online.

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