Review

Treating polyarteritis nodosa: current state of the art

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Received on April 3, 2011; accepted in revised form on April 4, 2011.

Clin Exp Rheumatol 2011; 29 (Suppl. 64): S110-S116.

Key words: polyarteritis nodosa, vasculitis, therapy, cyclophosphamide, hepatitis B

Competing interests: none declared.

ABSTRACT

Defining treatment guidelines for polyarteritis nodosa (PAN) is complicated by the evolving definition and classification of this vasculitis, and because clinical trials have included patients with PAN, microscopic polyangiitis or, sometimes, Churg-Strauss syndrome. Nonetheless, clinical trial data support that the "idiopathic generalised" form of PAN benefits from a severity-adapted treatment strategy, implying that cases with life-threatening manifestations require a regimen combining high-dose glucocorticoids and cyclophosphamide, whereas a non-severe disease may be treated with glucocorticoids alone. Results of uncontrolled studies indicate that hepatitis B virus-associated PAN management should include an antiviral agent, short-term glucocorticoids and plasma exchanges. No robust scientific evidence is available to guide the treatment of the limited variant "cutaneous PAN". Most experts recommend a less aggressive therapy with non-steroidal anti-inflammatory drugs or other agents, such as colchicine or dapsone. PAN has become an even more uncommon disease, probably due to classification changes and, perhaps also to a genuine modification of the epidemiology of this vasculitis. Although more data are needed to resolve outstanding questions, it is unclear whether all these matters can be studied in the future in large, sufficiently powered trials.

This review summarises the present state of the art of polyarteritis nodosa (PAN) therapy. In light of the changed definition of PAN and the possible repercussions these changes may have on clinical studies, the first part of this review revisits the definition and classification of PAN, and its current clinical, epidemiological and prognostic characteristics. Thereafter, the results of clinical trials and other treatment data for the 3 major clinical categories of PAN, namely "idiopathic generalised PAN", "virus-associated PAN" and "cutaneous PAN", are addressed.

PAN definition and classification

Despite being the most ancient vasculitic entity described, PAN has progressively evolved into a quite rare disease with somewhat blurred boundaries. Over the almost 150 years since its seminal description (1), the "clinical gestalt" of PAN has undergone many adjustments as a consequence of the discrimination of other vasculitis types, *e.g.* Wegener's granulomatosis (2), Churg-Strauss syndrome (3) and Kawasaki disease (4), which were split off from PAN. In the early 1990s, the Chapel Hill Consensus Conference (CHCC) for the nomenclature of systemic vasculitides introduced a major change by separating microscopic polyangiitis as a distinct entity. PAN was then defined as a vasculitis exclusively involving medium-sized vessels, *i.e.* medium-sized and small arteries (5).

In clinical practice, characterisation of medium-sized-vessel inflammation has emerged as the unique and essential criterion for PAN diagnosis. This essentially histopathology-based concept reflects that PAN has neither pathognomonic clinical features nor a biomarker that can be used to reliably differentiate it from other vasculitides. However, for a subset of cases with involvement of the gastrointestinal tract or kidneys, angiographic documentation of microaneurysms represents an accepted surrogate for histopathological proof of medium-sized-vessel vasculitis (6). Thus, PAN diagnosis in clinical practice faces some potential difficulties. The likelihood of seeing medium-size-vessel vasculitis probably varies with the anatomic site

Table I. Definitions and classification criteria for PAN.

1990 American College of Rheumatology classification criteria (32)*

1. Weight loss ≥4 kg
2. Livedo reticularis
3. Testicular pain or tenderness
4. Myalgias, weakness, or leg tenderness
5. Mononeuropathy or polyneuropathy
6. Diastolic blood pressure >90 mm Hg
7. Elevated blood urea nitrogen or creatinine
8. Hepatitis B virus
9. Arteriographic abnormality
10. Biopsy of small or medium-sized artery containing polymorphonuclear neutrophils

Chapel Hill Consensus Conference for the nomenclature of systemic vasculitides (5)

"Necrotising inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules."

European Medicines Agency (EMA) Classification Algorithm (9)

"Clinical diagnosis of primary systemic vasculitis (PAN, Wegener's granulomatosis, macroscopic polyangiitis or Churg-Strauss syndrome *and* non-fulfillment of classification criteria for entities other than PAN *and* histology compatible with the Chapel Hill Consensus Conference PAN or typical angiographic features."

*3 of the 10 criteria must be met for classification: 82.2%sensitivity, 86.6% specificity.

and type of biopsy, and the inflammatory process itself may complicate the full appreciation of the original calibre of an inflamed vessel. In addition, the view that histological evidence of concurrent small-vessel involvement is irreconcilable with PAN (5) is debatable and is a potential further source of inconsistency among pathologists in arriving at a diagnosis of PAN.

Mirroring the difficulties of defining PAN, none of the available PAN-classification systems gives full satisfaction (Table I). The 1990 American College of Rheumatology (ACR) criteria for PAN relied on a list of 10 mainly clinical and laboratory variables, but achieved only suboptimal performance characteristics and had the fundamental shortcoming of being developed prior to the separation of microscopic polyangiitis from PAN (7). A recently developed set of "diagnostic criteria" suggested that the use of negative criteria, *e.g.* no anti-neutrophil cytoplasm antibodies (ANCA) or no cryoglobulinemia, enhanced the sensitivity and specificity of PAN classification compared to the ACR criteria (8). The "European Medicines Agency (EMA) classification algorithm", in which several sets of ACR criteria and CHCC definitions are applied in a structured order, probably represents the most comprehensive approach to classifying PAN. Thus, PAN classification is based on the prior exclusion of other vasculitides *and* positive histology compatible with the CHCC definition of PAN or typical angiographic features (9).

Clinical variants of PAN

In addition to the systemic idiopathic form (henceforth called "idiopathic generalised PAN"), the PAN spectrum includes 2 well-accepted clinical variants, namely "hepatitis B virus (HBV)-associated PAN" and "cutaneous PAN". These clinical forms are important to recognise because of their specific therapeutic implications (Fig. 1).

In 1970, a substantial portion of PAN patients tested positive for active HBV infection (10, 11). The discovery that HBV induced a subset of PAN cases was a major step forward in understanding PAN pathogenesis. This so-called HBV-associated PAN variant appeared to be mediated by the deposition in blood vessels of immune complexes formed between viral antigens and antibodies during the early stages of HBV infection. Comparisons of HBV-associated and idiopathic PAN indicated that the former may have a more full-blown disease presentation. No specific classification system exists for this PAN subgroup. Notably, for a patient with PAN and positive HBV serology, recent infection and active virus replication suggest that both events are causally linked rather than a coincidental association. Whether PAN is also associated with hepatitis C virus infection remains less clear, although case series describing that association have been published (12).

Cutaneous PAN became known in 1931 (13) as a skin-restricted form of medium-sized-vessel vasculitis exclusively involving the limbs and predominantly the area below the knees (14-16). Although the skin is the predominantly affected tissue, local extracutaneous manifestations, such as arthralgias, arthritis, myalgias and neuropathy, may be seen (16). Any potential connection between cutaneous and generalised forms of PAN is poorly understood. Progression from cutaneous PAN to idiopathic generalised PAN exceptionally occurs but has been described (16), thereby suggesting that the two forms belong to the same entity. Definitive diagnosis of cutaneous PAN relies on clinical findings and histopathological evidence of medium-sized-vessel vasculitis. Deep incisional skin biopsies are required because the involved vessels are located in the deep dermis and subcutaneous tissue (16).

Epidemiology of PAN

PAN has become an even more uncommon disease and a rare form of vasculitis, but its precise frequency is difficult to determine. While a true change of PAN epidemiology cannot be excluded, there is little doubt that the current rarity of PAN is largely explained by the gradual narrowing of the place allocated to it in the spectrum of systemic vasculitides. Reported prevalence and annual incidence estimates for PAN ranged, respectively, from 2–33 (17-21) and 0–16 per million (20, 22-26). These numbers probably reflect divergences in the criteria used to define PAN, but also indicate that it is among the least common forms of systemic vasculitides. A large case series, including 348 cases of PAN diagnosed over a 43-year period, suggested that idiopathic generalised and HBV-associated PAN account for approximately two-thirds and one-third of the cases,

respectively. In addition, some observations indicate that HBV-associated PAN might be on the decline (27). The true frequency of cutaneous PAN in the general population is not known, but the largest published case series of this variant included 79 patients (28). The aetiology of cutaneous PAN remains unknown, although a number of triggering factors, *e.g.* streptococcal infection, tuberculosis or adverse drug reactions, have been advanced (16).

Prognostic factors for PAN

Because idiopathic generalised PAN and HBV-associated PAN have markedly varied clinical presentations, efforts have been made to identify clinical predictors of increased risks of mortality in PAN patients, with the idea in mind of tailoring treatment to one's individual needs.

Several survival analyses provided insight into the factors associated with higher mortality risks in PAN patients. Based on a retrospective study involving 342 subjects with PAN, microscopic polyangiitis or Churg-Strauss syndrome, renal disease (defined as proteinuria and/or impaired renal function), severe gastrointestinal signs (*e.g.* pancreatitis, perforation, haemorrhage or peritonitis), severe cardiac manifestations (*e.g.* left heart failure) and/or central nervous system involvement predicted higher mortality (29). In multivariate analyses, severe gastrointestinal symptoms and proteinuria were independent predictors of shorter survival. These observations defined the Five Factor Score and suggested that PAN, microscopic polyangiitis or Churg-Strauss syndrome patients with renal, severe gastrointestinal, severe cardiac and/or central nervous system manifestations should be considered an increased risk of death (29).

Recent revision of that score slightly modified the list of factors predicting death (30). The new survival analyses, based on an extended cohort of more than 1,100 subjects also including cases with Wegener's granulomatosis, identified 2 additional variables, *i.e.* age, and the absence of ear, nose and throat disease, as markers of an increased risk of death. Conversely, a central nervous system disease was no longer retained and only creatininemia ≥150µmol/l, but not proteinuria, was retained from among the renal markers. Subgroup analyses stratified by aetiology indicated that, among the 349 individuals with idiopathic generalised or HBV-associated PAN, older age and gastrointestinal involvement predicted a higher risk of mortality (30). Only a few other small studies analysed factors heralding an enhanced risk of death (31).

While those analyses provided valuable help in understanding the factors predicting poorer prognoses, the approach used is limited in that it focused exclusively on mortality. Peripheral neuropathy is sometimes also associated with severe clinical symptoms compromising quality of life. Moreover, uncommon but life-threatening manifestations might not have been captured by those analyses. Therefore, additional individual-level features may have to be considered in judging a patient's risk profile.

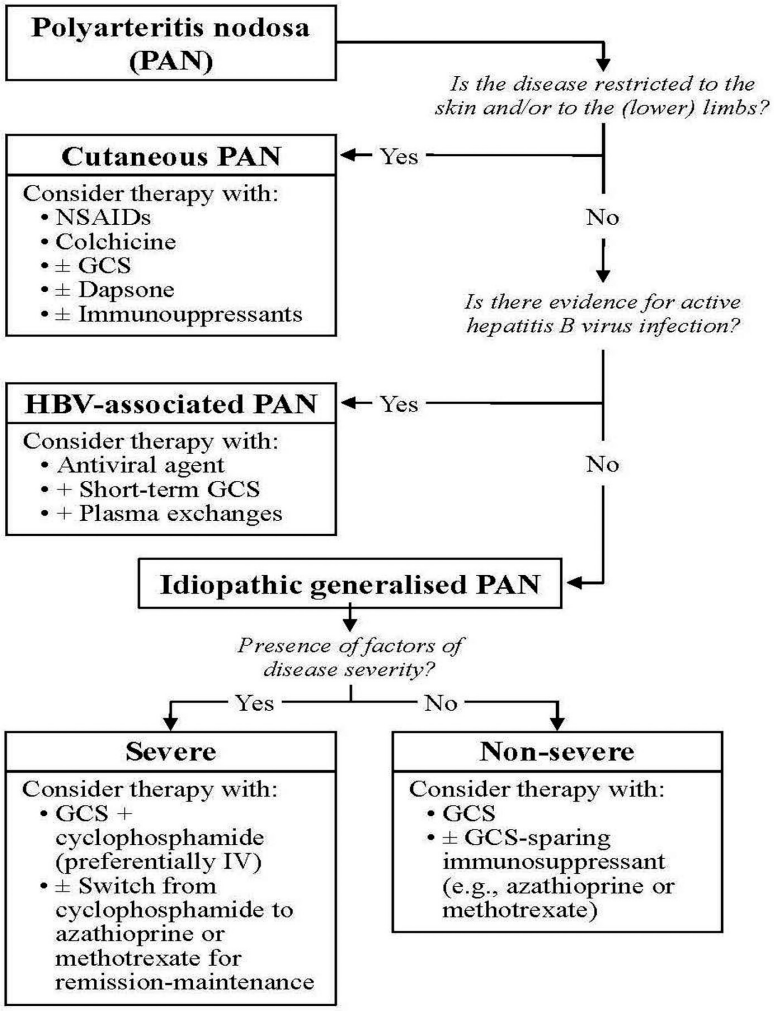

Fig. 1. Algorithm for the treatment of polyarteritis nodosa.
GCS: glucocorticoids, IV: intravenous, NSAIDs: non-steroidal anti-inflammatory drugs.

Treatment of idiopathic generalised PAN

A substantial body of information on PAN therapy has accumulated from clinical trials (Table II) and longitudinal cohort studies. Most of those studies were conducted by the same collaborative investigator network, the French Vasculitis Study Group. This situation, with a prominent study group contributing to the bulk of available evidence, likely reflects the remarkable attention those investigators have devoted to PAN.

Discerning how to treat PAN is also somewhat hampered by the available research. Many clinical trials or co-

Table II. Summary of published clinical trials addressing polyarteritis nodosa (PAN).

First author, year (ref.)	Design	Diseases studied	No. PAN/no. total cases	Subset analysed	Investigated treatment regimen
Guillevin, 1991 (39)	OL-RCT	PAN, CSS	NS/71	All	GCS alone *vs*. GCS + adjunctive CYC
Guillevin, 1992 (43)	OL-RCT	PAN, CSS	60/78	Non-severe	GCS alone *vs*. GCS + adjunctive PE
Guillevin, 1995 (44)	OL-RCT	PAN, CSS	48/62	Severe	GCS alone *vs*. GCS + adjunctive PE
Gayraud, 1997 (41)	OL-RCT	PAN, CSS	17/25	Non-severe	GCS + IV CYC *vs*. GCS + oral CYC
Guillevin, 2003 (42)	OL-RCT	PAN, MPA	18/65	Severe	GCS + 6 CYC pulses *vs*. GCS + 12 CYC pulses
Ribi, 2010 (45)	OL-RCT	PAN, MPA	58/124	Non-severe	GCS + 2nd-line CYC *vs*. azathioprine
Guillevin, 1993 (47)	Uncontrolled	HBV-PAN	33/33	All	Vidarabine + GCS + PE
Guillevin, 1994 (48)	Uncontrolled	HBV-PAN	6/6	All	Interferon-2α + GCS + PE
Guillevin, 2004 (49)	Uncontrolled	HBV-PAN	10/10	All	Lamivudine + GCS + PE

CSS: Churg-Strauss syndrome, CYC: cyclophosphamide, GCS: glucocorticoids; HBV: hepatitis B virus, IV: intravenous, MPA: microscopic polyangiitis, NS: not stated, OL-RCT: open-label, randomised-controlled trial, PE: plasma exchange.

hort studies were designed or mounted before the final designation of microscopic polyangiitis as an individual entity. Moreover, investigators continued to pool PAN with microscopic polyangiitis and Churg-Strauss syndrome, hypothesising that, despite their different pathophysiologies, these entities should be treated similarly. Although representing the best scientific evidence available to date, the question persists whether those findings can be reconciled with the current PAN definition.

1. Combination therapy with glucocorticoids and cyclophosphamide

Idiopathic generalised PAN is a chronic and potentially life-threatening disease, which often runs a relapsing course. Therefore, the goal of PAN therapy is 3-fold and aims at preventing death, achieving sustained disease remissions and minimising treatment-related side effects and morbidity.

Glucocorticoids and cyclophosphamide represent the cornerstone of PAN therapy. The benefit of prescribing glucocorticoids to PAN patients was first reported in 1967 in a retrospective cohort study whose results indicated that this agent achieved considerably prolonged survival (32); those findings were subsequently confirmed (33, 34). Afterwards, it was reported that adding cyclophosphamide further prolonged survival rates, compared with glucocorticoids alone (33, 35). However, the benefit of cyclophosphamide on survival rates was questioned by the observations of other cohort studies that suggested either no such effect (36) or a positive effect only for those patients with a more severe disease (37, 38). Only 1 study assessed cyclophosphamide efficacy and safety in a randomised, open-label clinical trial on 71 patients diagnosed with PAN or Churg-Strauss syndrome. The results of that trial indicated that cyclophosphamide significantly increased the remission rate and reduced the relapse risk. A positive effect of adjunctive cyclophosphamide on lowering mortality could not be demonstrated (39).

In 2009, a group of experts representing various medical specialties published treatment recommendations for medium- and small-vessel vasculitides within the framework of the European League against Rheumatism (EULAR) (40). Based on the available literature, that group recommended combining glucocorticoids and cyclophosphamide to treat PAN and advised that cyclophosphamide could be given intravenously or taken orally daily (40). Commonly prescribed cyclophosphamide doses are 2mg/kg/day for oral use or 600mg/m^2 given at 2–4 week intervals for intravenous pulse therapy. Dose adjustments need to be considered for elderly patients or those with impaired renal function.

Intermittent intravenous and daily oral cyclophosphamide administration were compared in a randomised clinical trial in patients with PAN or Churg-Strauss syndrome (41). That study did not find a statistically significant difference regarding the main efficacy outcomes according to the administration route, but the intravenous regimen resulted in fewer side effects (41).

The duration of immunosuppressive therapy was evaluated in a clinical trial that randomised patients with severe PAN or microscopic polyangiitis to receive either a shortened, 6-pulse cyclophosphamide regimen (administered over 4 months) or a 12-pulse regimen (given over 10 months) (42). The shorter regimen resulted in a significantly higher relapse rate, and subgroup analyses suggested that those findings also held true for PAN patients alone, suggesting that PAN should be treated with cyclophosphamide for longer than 4 months (42).

Two randomised clinical trials on PAN and Churg-Strauss syndrome patients assessed the usefulness of adding plasma exchanges to glucocorticoids (43) or combined glucocorticoid-cyclophosphamide therapy (44). Those studies consistently failed to demonstrate an additional benefit of plasma exchanges with respect to the primary composite outcome of disease-free survival. Whether plasma exchange could be useful in special situations of idiopathic generalised PAN, such as acute renal failure, remains elusive.

2. Severity-adapted therapy

Agreement is virtually universal that therapy combining high-dose glucocorticoids with cyclophosphamide is mandatory for idiopathic generalised PAN with potentially life-threatening organ involvement. In this patient subset, the substantial risk of death justifies this therapeutic strategy and outweighs the increased infectious, carcinogenic and gonadal toxicities of immunosuppressive agents.

In contrast, it remains controversial whether cyclophosphamide use is necessary for all patients. Indeed, it was suggested that glucocorticoids alone sufficed as a first-line therapy for patients with no manifestations of serious organ involvement. Although not yet confirmed by controlled-trial results, this paradigm is supported by data from retrospective cohort studies. Compared to glucocorticoids alone, cohort analyses indicated that a survival benefit was obtained with adjunctive cyclophosphamide therapy only for the subset of patients with severe PAN (37, 38).

Treatment of newly diagnosed cases with non-severe idiopathic generalised PAN with glucocorticoids alone has repeatedly been applied in clinical trials (41, 43, 45). In those trials, the applied glucocorticoid protocol was based on starting prednisone at 1mg/kg/day with subsequent tapering off over 9–12 months. An immunosuppressant was prescribed only to patients not achieving remission or experiencing a disease flare.

A randomised-controlled trial evaluated which immunosuppressant should be given to patients with non-severe idiopathic generalised PAN or microscopic polyangiitis who failed to respond to, or who relapsed after, first-line therapy with glucocorticoids alone. Patients were randomised to receive either 6 cyclophosphamide pulses or daily azathioprine for 6 months at the time of a first relapse or glucocorticoid-monotherapy failure (45). Among the 124 patients enrolled, 58 patients were classified as having PAN. After a mean observation period of 5.2 years, sustained disease remission, relapses and treatment failures were recorded for 40%, 39% and 21% of the patients, respectively. Among those randomly assigned to receive second-line rescue therapy with cyclophosphamide or azathioprine, both treatment groups performed equally well in terms of survival, disease remission and subsequent relapse risk (45).

The relatively high relapse and treatment-failure rates perpetuate the question as to whether an immunosuppressant should be prescribed systematically in addition to glucocorticoids to patients with non-severe, idiopathic generalised PAN. A definitive answer might come from an ongoing, double-blind, randomised, placebo-controlled clinical trial designed to evaluate the efficacy and safety of adjunctive azathioprine in newly diagnosed, non-severe idiopathic generalised PAN (ClinicalTrials.gov: NCT00647166).

3. Unresolved questions

A number of outstanding questions remain concerning treatment of idiopathic generalised PAN. Once disease remission is obtained, replacing cyclophosphamide by a less toxic maintenance agent, such as azathioprine or methotrexate, has become the standard-of-care for Wegener's granulomatosis and microscopic polyangiitis, but this scheme has not yet been explored for PAN. It can be argued that this approach could reasonably be extrapolated to idiopathic generalised PAN to reduce the potential for cyclophosphamide-induced toxicities. Whether biologics, *e.g.* monoclonal anti-CD20 agents (46), would be effective against idiopathic generalised PAN is hypothetical. Further areas of uncertainty pertain to the management of severe idiopathic generalised PAN refractory to first-line therapy.

Treatment of HBV-associated PAN

The identification of HBV-associated PAN stimulated the development of an aetiology-based therapeutic strategy including an antiviral compound. The rationale underlying this approach is that the control of the viral infection would cure the vasculitic manifestations. Glucocorticoid administration was restricted to the initial treatment phase, and plasma exchanges were added to clear the immune complexes until recovery from active HBV infection. To date, HBV-associated PAN represents the first and almost sole vasculitis model for which an aetiology-based therapy has been widely utilised.

This treatment concept was never evaluated in a controlled trial, but several prospective uncontrolled trials provided persuasive evidence of its effectiveness. Paralleling the advent of increasingly potent agents to treat HBV, studies successively explored vidarabine (47), interferon-2α (48) and lamivudine (49) treatment of HBV-associated PAN. In all 3 studies, glucocorticoids were given at an initial dose of 1mg/kg/day for only 2 weeks. Plasma exchanges were maintained until HBV replication resolved or for a maximum of 2–3 months. A virological response, defined as HBe antigen-to-HBe antibody seroconversion, was obtained in 35% (47) to 67% (48-49) of the investigated patients and prolonged vasculitis control in 90–100% (47, 49).

The long-term outcome of a 115-patient cohort with HBV-associated PAN was analysed (50). Those data confirmed that among the virological responders, PAN sensibly never relapsed. Moreover, a subset of patients did not enter remission, and it remains unclear how to manage HBV-associated PAN failing to respond to this therapy. Possible options include the combination of 2 antiviral agents, although control of some patients' vasculitides requires standard immunosuppressive therapy. Pertinently, more recently published observations on the treatment of the subset of patients with active hepatitis C virus-associated PAN have indicated that many of them were successfully treated with a very similar approach including ribavirin, an antiviral drug active against that aetiological pathogen (12).

Treatment of cutaneous PAN

No strong evidence-based recommendations exist for the treatment of cutaneous PAN. Clinical trials for this PAN variant are lacking, and guidance for treatment can only be derived from case series or case reports.

Because cutaneous PAN does not threaten any major organ function, the general consensus is that treatment does not need to be as intense as that for idiopathic generalised PAN. First-line therapy with salicylates or other non-steroidal anti-inflammatory drugs (14, 16) or colchicine (16) is widely recommended. Cutaneous PAN symptoms often respond well to therapy, and treatment can be withdrawn within several weeks. However, definitive disease remission is difficult to obtain, and patients with cutaneous PAN frequently experience recurrent acute vasculitis

flares. For these patients, moderate-to-high dose glucocorticoids (0.5 to 1mg/kg/day of oral prednisone) and/or a variety of other medications, such as dapsone, hydroxychloroquine, pentoxyfilline, intravenous immunoglobulins (14-16) or infliximab (51), have been reported to be effective. Azathioprine, methotrexate or cyclophosphamide in combination with high-dose glucocorticoids are reserved for severe or refractory cutaneous PAN (16).

Conclusions

Its evolving definition and classification, its rarity, and the pooling of PAN and other vasculitides in clinical studies, have complicated the formulation of evidence-based principles for PAN therapy.

With these considerations in mind, evidence supports that idiopathic generalised PAN with severe life-threatening or potentially incapacitating manifestations should be treated with a regimen combining glucocorticoids and cyclophosphamide. However, cyclophosphamide may not be mandatory for all cases of non-severe idiopathic generalised PAN, and first-line glucocorticoid monotherapy has been given repeatedly and successfully in controlled trials to these patients. Clinical trial data also support intermittent intravenous cyclophosphamide as an equally effective but safer administration route than daily oral intake. Treatment of HBV-associated PAN involves a different approach, centred on the use of an antiviral agent aimed at controlling the infection. Therapy for cutaneous PAN remains ill-defined but calls for a less aggressive approach based on non-steroidal anti-inflammatory drugs given over short time periods and, if any, additional anti-inflammatory medications.

More high-quality research is needed to fill the gaps in our current knowledge on the best care for PAN patients. Treatment duration, the adequacy of using immunosuppressive agents less toxic than cyclophosphamide – either to replace the latter to maintain severe disease in remission or as glucocorticoid-sparing for non-severe disease – and the management of refractory disease are areas of persistent uncertainty. Today, research on PAN faces the paramount limitation of a disease that now appears to be much more uncommon than was thought several decades ago. Therefore, caregivers may increasingly have to integrate therapeutic advances gained from other vasculitides into treatment decision-making for PAN patients.

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