Role and place of methotrexate in vasculitis management

Methotrexate is a folic acid analog with a favorable efficacy-to-toxicity ratio that has been used for many years to treat a variety of inflammatory arthropathies, thereby explaining the growing interest in its use for systemic vasculitides. For giant cell arteritis or Takayasu's arteritis patients, methotrexate can be given to those at high risk of developing corticosteroid-related side effects, or those with relapsing or refractory disease despite corticosteroid use. Clinical studies have yielded mixed results regarding its adjunction to corticosteroid as first-line therapy for giant cell arteritis. Such prospective studies for Takayasu's arteritis are needed, but several patients with highly active or extensive disease already benefit from this combination as first-line therapy. For Wegener's granulomatosis, methotrexate can be combined with corticosteroid as induction therapy for localized forms. For microscopic polyangiitis, and more severe or generalized Wegener's granulomatosis forms, it was recently demonstrated to be as effective as azathioprine in maintaining remission. Methotrexate is generally considered to have a relatively good safety profile, but close surveillance during follow-up is necessary to detect its potential hematologic, pulmonary and hepatic toxicity. However, it should be prescribed with caution or avoided in vasculitis patients with impaired renal function.

KEYWORDS: antineutrophil cytoplasmic antibody-associated vasculitis ■ azathioprine ■ giant cell arteritis ■ methotrexate ■ vasculitis ■ Wegener's granulomatosis

Christian Pagnoux[1†] & Michelle Goulet[2]

[†]Author for correspondence:
[1]Department of Internal Medicine, National Referral Center for Necrotizing Vasculitides and Systemic Sclerosis, Hôpital Cochin, Assistance Publique – Hôpitaux de Paris, Université Paris Descartes, 27, rue du faubourg Saint-Jacques, 75679 Paris Cedex 14, France
Tel.: +33 158 411 461
Fax: +33 158 411 450
christian.pagnoux@cch.aphp.fr
[2]Hôpital Sacré-Cœur de Montréal, Université de Montréal, Montréal (QC), Canada

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Learning objectives

Upon completion of this activity, participants should be able to:

- Describe the prevalence of different adverse effects associated with methotrexate
- Describe the recommendations for monitoring treatment with methotrexate
- Identify the types of systemic vasculitides
- Identify vasculitides for which methotrexate is recommended as first-line treatment

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Author & Credentials

Christian Pagnoux, *MD, MPH, Department of Internal Medicine, National Referral Center for Necrotizing Vasculitides and Systemic Sclerosis, Hôpital Cochin, Assistance Publique – Hôpitaux de Paris, Université Paris Descartes, Paris, France*

Disclosure: Christian Pagnoux, MD, MPH, has disclosed no relevant financial relationships.

Michelle Goulet, *MD, FRCP, Hôpital Sacré-Cœur de Montréal, Université de Montréal, Montréal (QC), Canada*

Disclosure: Michelle Goulet, MD, FRCP, has disclosed no relevant financial relationships.

CME Author

Désirée Lie, *MD, MSEd, Clinical Professor, Department of Family Medicine, University of California, Irvine; Director, Division of Faculty Development, UCI Medical Center, Irvine, California*

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Methotrexate (MTX) is a very well-known drug owing to its use for treating rheumatoid arthritis, since the early 1950s, with proven benefits [1–4]. It took almost two decades before MTX started being prescribed for vasculitides [5,6]. Several studies have subsequently helped to clarify its indications, optimal dose and regimen, especially for Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA). However, many questions remain to be answered, especially as to its place as a first-line therapy in combination with corticosteroids (CS) for large-vessel vasculitides.

Mechanisms of action, metabolism & pharmacology of methotrexate

Methotrexate mechanisms of action are only partially known and understood. MTX is an antimetabolite and a folate analog with only minor structural differences, designed to compete for folate receptors. It enters cells through an active transport mechanism and by facilitated diffusion, and once inside the cell, it is converted into polyglutamate MTX by folylpolyglutamyl synthase. Polyglutamate MTX reversibly inhibits dihydrofolate reductase but also inhibits other enzymes, especially thymidylate synthase and 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase. Reduced folate (tetrahydrofolate [THF]) is involved in the *de novo* synthesis of purine and pyrimidine precursors of DNA and RNA [7]. THF is also important for the methylation of DNA, RNA and other proteins, such as homocysteine. Ultimately, MTX is eliminated from the cell by transporters of the ATP-binding cassette family.

Methotrexate is able to inhibit proliferation and/or induce apoptosis of neoplastic cells and was therefore first used at the end of the 1940s by hematologists. Indeed, MTX also possesses a variety of anti-inflammatory effects at low doses, that is, those prescribed by rheumatologists. MTX inhibits T-cell activation and proliferation, downregulates the expression of some activation and adhesion molecules, for example, intercellular adhesion molecule-1, decreases immunoglobulin production, inhibits cyclooxygenases and lipooxygenases, and modulates monocyte and macrophage secretion of various cytokines. Most of these anti-inflammatory effects probably reflect the inhibition of AICAR transformylase, causing the accumulation of AICAR, and thus enhancing adenosine release into the blood. Extracellular adenosine can bind to transmembrane-spanning adenosine surface receptors, especially types A2a and A3, resulting in the subsequent inhibition of phagocytosis, lymphocyte proliferation, and altered synthesis and/or secretion of several proinflammatory cytokines, such as TNF-α, IL-12 and IFN-γ.

For its rheumatologic indications, MTX is usually administered at a weekly dose of 0.2–0.3 mg/kg, for example, 10–25 mg/week, most frequently administered orally, or injected intramuscularly or subcutaneously. For inflammatory myopathies, higher doses of up to 40 mg/week are generally prescribed. Regardless of the route and dose, its bioavailability is good, reaching 90% when given subcutaneously and up to 75% when taken orally, but it may be more variable with oral doses over 25 mg/week [8]. MTX is eliminated through the kidneys with nonlinear kinetics due to its tubular secretion–reabsorption cycle, which can be altered in renal insufficiency or certain conditions, such as with the coprescription of high-dose aspirin, thereby potentially increasing its toxicity. Notably, the dose administered more closely parallels its toxicity than its efficacy, and adverse events can occur before the expected therapeutic benefit of MTX [9]. Indeed, there is a latent period of several weeks before the MTX efficacy in patients can be appreciated and evaluated [10,11].

Adverse events are the main factor influencing the decision to discontinue MTX; they can be minor, for example, gastrointestinal intolerance (occurs in up to 70% of the patients) [12–14], or more severe, like pancytopenia (occurs in 0.9–1.4% [13,15–18] or liver cirrhosis (occurs in 0–2%) [19,20]. Indeed, 10–37% of patients terminate MTX treatment owing to an adverse event. Potential and more important adverse events of MTX to keep in mind, along with its contraindications, are summarized in **Table 1 & Box 1**. Some MTX adverse events are due to folate antagonism and closely resemble those seen in patients with folate deficiency, such as elevated erythrocyte mean corpuscular volume or folate-deficiency anemia. Thus, folate supplementation allowed 83% of patients with rheumatoid arthritis to continue MTX at 48 weeks in the study by van Ede *et al.*, compared with 62% of those receiving MTX without supplementation ($p < 0.001$, with either folic or folinic acid) [21]. However, while there is a basis for using folate supplementation to reduce adverse effects, the results of some studies suggested that adding folic acid to MTX could lead to a small loss of efficacy, due to their competition and interferences [4,10,21–23]. However, the meta-analysis by Ortiz *et al.* did not demonstrate the consistent influence of such folate

Table 1. Potential adverse events of methotrexate in rheumatic diseases.

Adverse event	Estimated frequency (%)	Additional notes
Overall	73–85	–
Gastrointestinal		
Stomatitis	5–30	–
Other digestive complaints – Nausea – Anorexia – Abdominal pain	20–70	Parenteral treatment is usually better tolerated
Hepatic		
Elevated transaminases Fibrosis Cirrhosis	70–88 3–35 0–2	In most cases is <2–3 times the upper limit of normal and regresses spontaneously or with temporary discontinuation Possibly less common in rheumatoid arthritis than in vasculitis Risk factors include high cumulative MTX dose and duration of therapy, older age, alcohol intake, obesity, diabetes, pre-existing liver disease and/or kidney failure(s)
Allergy		
Rash	5–7	High recurrence rate on resumption of therapy
Hypersensitivity syndrome	Rare	Typically occurs after repeated administrations
Anaphylaxis	Rare	Usually after multiple and high doses in an oncology setting
Other cutaneous		
Nodules	8–11	Incidence is lower in vasculitis than rheumatoid arthritis Dose reduction may be useful Strong correlation with the *HLA-DR1B*0401* allele
Alopecia	10	–
Hematologic		
Macrocytosis	22	May precede or indicate increased risk of cytopenias
Cytopenias – Leukopenia – Thrombocytopenia – Pancytopenia	 10–25 1.8–4.1 0.9–1.4	Dose reduction or temporary discontinuation may be useful Risk factors include renal failure, folate deficiency, polymedication, older age and/or hypoalbuminemia Avoid concomitant use of cotrimoxazole
Infections		
Severe	8.3	–
Pulmonary		
Cough, exertional dyspnea	25	Usually nonprogressive and resolves with discontinuation
Acute interstitial pneumonitis	0.3–7.5	Usually occurs early during the course of treatment since it is thought to be immunoallergic No correlation with weekly or cumulative dose, but pre-existing lung disease may be a risk factor Permanent withdrawal is advised
Interstitial fibrosis	Rare	–
Pulmonary nodules	Rare	–
CNS		
General malaise, fatigue	20–30	Recurs regularly within 24 h of last dose
Headache	4–11	–
Dizziness, vertigo	5	–
Cognitive impairment	2	–
Severe encephalopathy	15	Mainly reported with parenteral high-dose or intrathecal administration
Oncologic		
Cancer	Sporadic	Most probably a fortuitous association
Lymphoma	Rare	–

MTX: Methotrexate.
Data from [10,12,13,15–20,28,56,102–124].

Table 1. Potential adverse events of methotrexate in rheumatic diseases (cont.).

Adverse event	Estimated frequency (%)	Additional notes
Other		
Osteopathy	Rare	No adverse effect on bone density with doses used in vasculitis Usually with high doses in an oncology setting
Teratogenesis and fetal loss	Unknown	Extremely rare but effective contraception mandatory

MTX: Methotrexate.
Data from [10,12,13,15–20,28,56,102–124].

supplementation on disease activity [4]. No consensus exists regarding the dose and frequency of folate supplementation. In any case, it seems important to delay folate supplementation for 48 h after MTX administration, because the timing of the folic or folinic acid intake in relation to MTX might, at least in part, influence MTX efficacy [24].

Baseline and serial complete blood counts, and determination of creatinine level, aspartate aminotransferase, alanine aminotransferase and albumin are recommended every 2–4 weeks for the first 3 months of therapy and after each dose increment, then every 8–12 weeks for the 3 following months, and every 12 weeks thereafter [20,25]. Older patients and/or those with alcohol dependence, multiple underlying diseases or comorbidities, especially chronic hepatitis or renal impairment, should be monitored more closely if MTX is not already contraindicated.

Dosage of serum MTX levels lack reliability for predicting adverse events, and that of its intracellular polyglutamate metabolites is technically difficult and not widely available. Methylene THF reductase (MTHFR) is not directly inhibited but is influenced by MTX effects on the intracellular folate pool. The presence of either the heterozygous or homozygous C677T mutation in the *MTHFR* gene leads to further homocysteine accumulation and is associated with increased risk of elevated transaminases, hairloss or gastrointestinal symptoms during MTX treatment, and ultimately, the necessity to stop MTX [26,27]. The homozygous or heterozygotes C677T variants have respective prevalences of 8–10% and 40% in the general population. Conversely, the C allele of the A1298C polymorphism was found to be associated with better efficacy in rheumatoid arthritis, at least when compared with another 1298A/A homozygous genotype [27]. However, because determination of *MTHFR* genotype is not yet widely available in every clinical facility, and because MTX metabolism seems to be influenced by many gene products [11,28], cost–effectiveness studies have to demonstrate the advantages of MTX pharmacogenetic assays over simple patient follow-up with serial monitoring.

Box 1. Contraindications to methotrexate use.

Infectious
- Active bacterial infection
- Active herpes zoster
- Life-threatening fungal infection
- Active tuberculosis
- Latent tuberculosis before initiation of preventive therapy

Pulmonary
- Interstitial pneumonitis (rheumatoid arthritis-associated or of unknown cause)
- Clinically significant fibrosis

Hematologic & oncologic
- Leukopenia <3000/mm^3
- Thrombocytopenia <50,000/mm^3
- History of myelodysplasia
- Lymphoproliferative disease within the last 5 years

Liver
- Transaminases > twofold the upper limit of normal
- Acute hepatitis B or C
- Chronic hepatitis B or C, under treatment or not

Renal
- Creatinine clearance <30 ml/min

Reproductive
- Planning or current pregnancy
- No contraception for woman of child-bearing age
- Breastfeeding

Others
- Multiple sclerosis and other demyelinating disorders
- Allergy to methotrexate or its constituents

Data from [25,125].

Classification of systemic vasculitides

Systemic vasculitides can be classified according to the 1994 Chapel Hill nomenclature [29], which is based on the main clinical manifestations and caliber of the vessels predominantly affected (Figure 1). MTX has been evaluated and/or is often used to treat the two large-vessel vasculitides – that is, giant cell arteritis (GCA; sometimes also called temporal arteritis or Horton's disease) and Takayasu's arteritis (TA) – and three of the small-sized vessel vasculitides, that is WG, MPA and, but to a lesser degree, Churg–Strauss syndrome (CSS). Potential indication of MTX at some time and/or for

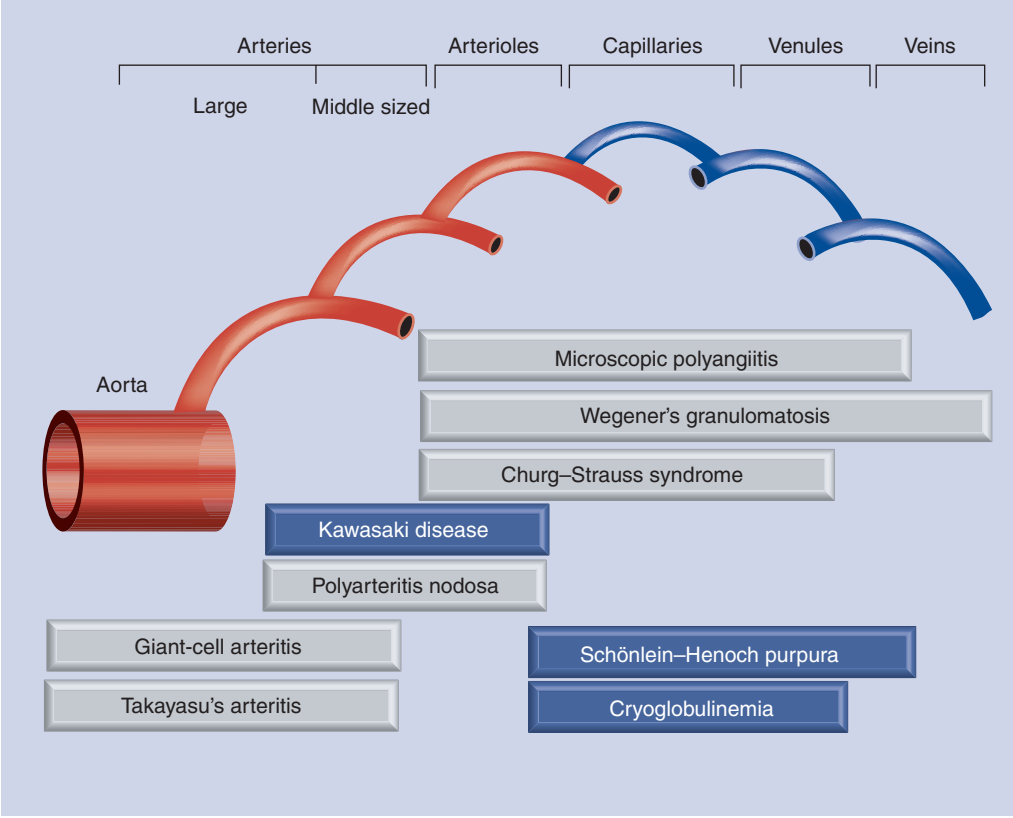

Figure 1. Chapel Hill nomenclature for systemic vasculitides. This classification distinguishes between large, medium-sized and small-vessel vasculitides. Darkened squares are vasculitides for which methotrexate has not been evaluated, is rarely prescribed at present and/or has no theoretical place.
Data from [29].

some patients with polyarteritis nodosa (PAN) will be reviewed, but the treatment for cryoglobulinemic vasculitis or Henoch–Schönlein purpura, in which MTX seems to have no, less, or only anecdotal place at present, will not be detailed herein.

Methotrexate for large-vessel vasculitides

Giant cell arteritis

Three randomized controlled trials (RCTs) have been conducted to evaluate the potential benefit of MTX adjunction to conventional CS therapy for newly diagnosed GCA patients. Their designs differ slightly and they yielded conflicting results. Indeed, only the Spanish study by Jover *et al.* demonstrated a significant benefit [30]. In that study, 42 patients with newly and biopsy-proven GCA received CS (60 mg/day oral prednisone for 2 weeks, then gradually tapered every 1–2 weeks until complete withdrawal) and either 10 mg/week oral MTX or placebo starting from diagnosis and for 2 years. The rate of patients who experienced at least one relapse was significantly lower for the MTX group (45% of MTX recipients vs 84.2% of placebo-arm patients; $p = 0.02$) and, thus, CS consumption could be lowered by more than 20% for MTX recipients (mean cumulative prednisone dose: 4187 ± 1529 mg vs 5489.5 ± 1396 mg for the placebo group, $p < 0.009$; mean prednisone duration: 29 vs 94 weeks with placebo, $p < 0.0016$). However, clinically, no significant between-group difference for the rate of CS-related side effects was observed.

Second, Hoffman *et al.* observed no benefit in their study on 98 patients, 79 of whom had biopsy-proven GCA, when MTX was prescribed orally at 0.15 mg/kg/week starting from diagnosis, and was progressively increased within 2 weeks to a maximum of 0.25 mg/kg/week or 15 mg/week for 1 full year after entering remission [31]. CS (prednisone) was prescribed at the initial dose of 1 mg/kg/day (not exceeding 60 mg/day), then progressively reduced by 5 mg every 4 days according to an alternate-day schedule until discontinuation after an approximate total duration of 6 months. Failure, defined as two distinct disease relapses or a relapse treated

with a 10-mg prednisone increase that did not achieve attenuation, was noted for 24.4% of MTX recipients versus 35.4% of the placebo-group patients at 6 months, and 57.5% versus 77.3% at 12 months, respectively (p = 0.26). No significant between-group differences for CS dose or duration were observed (5375 mg and 5.4 months for the MTX recipients vs 5275 mg and 5.6 months for the placebo group; p = 0.5).

Lastly, Spiera *et al.* studied 21 patients and were also unable to show any benefit of MTX given orally at a lower starting dose (7.5 mg/week, possibly increased to 20 mg/week) and initiated only after several weeks of CS administration, that is, when prednisone dose had been tapered to 30 mg/day [32]. Pertinently, cumulative CS doses and numbers of weeks to CS withdrawal were similar in both study arms (respectively: 6469 mg for MTX recipients vs 5908 mg for the placebo group, p = 0.6; 68 weeks for MTX recipients versus 60 weeks for the placebo arm, p = 0.5). Only one major relapse was recorded during the study period, in a MTX-treated patient.

However, Mahr *et al.* conducted a meta-analysis of these three trials using individual data and found that MTX was associated with a lower risk of relapse [33]. With a mean duration of follow-up of 54.7 weeks, they calculated hazard ratios for a first and second relapse of 0.65 (p = 0.04) and 0.49 (p = 0.02), respectively, for patients receiving MTX as compared with those taking the placebo. In addition, MTX afforded little CS-sparing of 842 mg for the cumulative dose at 48 weeks (p < 0.001), and approximately 1100 mg at 96 weeks (p = 0.007).

Based on these results, which remain controversial, it has been advanced, and even recommended by the European League Against Rheumatism (EULAR) [34], that MTX should be considered an adjunctive therapy for GCA (Table 2). However, in practice and at present, many physicians still use MTX only to treat GCA patients at high-risk of developing CS-related side effects, or those with relapsing, refractory and/or CS-dependent GCA, rather than as an adjunct to CS for first-line therapy. The optimal dosage is not clearly defined, but

Table 2. EULAR recommendations mentioning methotrexate for the therapeutic management of patients with systemic vasculitides.

Disease	Recommendations	Evidence level*	Notes
Large-vessel vasculitides (GCA and TA)	"We recommend that an immunosuppressive agent should be considered for use in large-vessel vasculitis as adjunctive therapy"	1A for GCA 3 for TA	Three RCTs of MTX adjunction to CS for GCA [30–32] with conflicting results, and one meta-analysis of those trials [33] demonstrating a modest role for MTX (10–15 mg/week) in containing relapse rate and cumulative CS-sparing MTX, used as an adjunct to CS for TA (20–25 mg/wk), may help to improve disease control and facilitate cumulative CS dose-sparing
Small- and medium-sized vessel vasculitides	"We recommend a combination of MTX (oral or parenteral) and CS as a less toxic alternative to CYC for the induction of remission in nonorgan-threatening or nonlife-threatening ANCA-associated vasculitis"	1B	MTX (20–25 mg/week) can be an alternative to CYC in patients with less severe disease and normal renal function and should be started at 15 mg/week and increased to 20–25 mg/week over the next 1–2 months, if tolerated; in a RCT [64], it was demonstrated to be equal to CYC in its capacity to induce remission It may take longer to achieve remission with MTX than CYC in patients with pulmonary involvement Patients on MTX may benefit from folic or folinic acid supplementation MTX should be monitored according to standard protocols
	"We recommend remission-maintenance therapy with a combination of low-dose CS therapy and, either AZA, LFL or MTX" (for ANCA-associated vasculitides)	1B for AZA 1B for LFL 2B for MTX‡	MTX (20–25 mg/kg/week) has been used effectively for maintenance therapy after induction of remission with CYC (if the serum creatinine is <130 µmol/l or 1.5 mg/dl)

**Level of evidence: 1A is for data coming from a meta-analysis of RCTs; 1B is for data from at least one RCT; 2A is for data from at least one controlled study without randomization; 2B is for data from at least one type of quasi-experimental study; 3 is for data from descriptive studies, such as comparative studies, correlation studies, or case–control studies; 4 is for data from expert committee reports or opinions and/or clinical experience of respected authorities.*

‡Evidence for MTX as a maintenance agent should now also be considered 1B, like AZA, since the WEGENT trial results, which showed that AZA and MTX have a similar efficacy for Wegener's granulomatosis and microscopic polyangiitis remission–maintenance, have been now published [75], after these recommendations were.

ANCA: Antineutrophil cytoplasmic antibody; AZA: Azathioprine; CS: Corticosteroids; CYC: Cyclophosphamide; EULAR: European League Against Rheumatism; GCA: Giant-cell arteritis; LFL: Leflunomide; MTX: Methotrexate; RTC: Randomized, controlled trial; TA: Takayasu's arteritis.

Adapted from the articles by Mukhtyar et al. [34,65].

10–15 mg/week of MTX might be sufficient for these patients, thereby yielding a relatively low risk of adverse event(s).

Takayasu's arteritis

Less data are available on TA. Notably, no RCT has been conducted on this vasculitis. Nonetheless, MTX is one of the most frequently prescribed immunosuppressants for these patients who relapse and/or are CS-dependent. In TA, MTX is usually given at the dose of 0.3 mg/kg/week, up to 15–25 mg/week [35–38].

The largest, prospective, observational study on 18 adults with relapsing or CS-dependent TA showed that remission was achieved after MTX adjunction for 13 (81%) of the 16 patients who did not rapidly drop out, and prolonged remission (mean: 18 months) for eight (50%) of them [35]. Other immunosuppressants have also been evaluated and could be used for refractory and/or relapsing TA, including cyclophosphamide (CYC), azathioprine (AZA), mycophenolate mofetil (MMF), leflunomide (LFL) and more recently, anti-TNF-α agents [39–46].

Because the frequency of refractory and/or relapsing TA clearly exceeds 20–25% [47–49], some authors suggested that MTX (or another immunosuppressant, such as AZA or CYC) could be useful for first-line therapy combined with CS, especially for those TA patients with diffuse arterial and/or highly inflammatory disease [50–52]. All six children from the recent pediatric study by Ozen *et al.* [53] received CS and an immunosuppressant as first-line therapy. Two of them had limited forms of TA – that is, only on one side of the diaphragm and without pulmonary involvement – and entered remission after receiving CS and oral MTX of 12.5 mg/m²/week, with follow-up lasting 3 months and 2 years, whereas three of the four remaining patients with more widespread disease entered remission with CS and oral CYC, followed by oral MTX for maintenance. This therapeutic strategy for first-line therapy, combining CS and an immunosuppressant, should probably be considered for TA, as recommended by EULAR (**Table 2**), but had a weaker evidence level than for GCA up to now [34].

Abatacept, a fusion protein of cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and the human immunoglobulin Fc fragment, designed to modulate the T-cell costimulatory signal mediated through the CD28–CD80/86 pathway, is also being evaluated in an ongoing pilot study on newly diagnosed TA (and GCA) patients (ClinicalTrials.gov number NCT00556439 [201]).

Methotrexate for Wegener's granulomatosis & microscopic polyangiitis

A distinction is made between WG patients with systemic, generalized or severe forms and those with localized, limited or early systemic forms. Indeed, the European group distinguishes several forms, mainly generalized and localized forms, while the North American group differentiates only between severe forms requiring CYC, and limited forms, which could be treated with combined CS and MTX instead of CYC (**Table 3**) [54].

Whether MPA patients can also be separated into these early systemic and severe subgroups, as defined by the EULAR/ European Vasculitis Study Group (EUVAS), and thus be treated differently, has been less studied to date. Conversely, it has been clearly demonstrated that MPA patients can be separated into two categories: those with one or more poor-prognosis factors according to the French five-factor score (FFS) (**Table 4 & Box 2**) [55], who must receive a combination of CS and an immunosuppressant to induce remission, mainly CYC at present, followed by maintenance therapy, like for WG; and those without any of these factors who can be treated with CS alone, reserving the adjunction of immunosuppressant for progressing and/or refractory disease despite CS.

Induction therapy for limited forms of Wegener's granulomatosis

For years, MTX use has been suggested as, and tested in several open-label studies [56–62], a potential induction agent, combined with CS, for WG patients with limited, localized and nonlife-threatening forms. MTX was usually given orally but its weekly dose varied greatly between studies, with starting doses ranging from 7.5 mg/week and further increased when necessary to 0.3 mg/kg/week. The precise MTX duration was not systematically reported but exceeded 1 year in all of the studies, when it was tolerated and effective. Reported remission rates ranged from 59 [61] to 78% [60]. Relapse rates ranged from 0%, for a subgroup of 20 WG patients with glomerulonephritis [63], to 10% in the study by Hoffman *et al.* [59], and to a maximum of 66% in the more recent of these studies by Villa-Forte *et al.* [60], possibly because of slightly different definitions for mild WG, minor/major relapses and/or MTX and CS dose regimens. The mean or median duration of remission before relapse was 20 [60] to 29 [58] months, and relapses mostly occurred after stopping MTX.

Table 3. Definitions of disease stage and subgroup forms of Wegener's granulomatosis.

	Clinical subgroup						
	EULAR/EUVAS definitions					*WGET/VCRC definitions*	
	Localized	***Early systemic***	***Generalized***	***Severe***	***Refractory***	***Limited***	***Severe***
Definition	Upper and/or lower respiratory tract disease without any other systemic involvement or constitutional symptoms	All, but without organ- or life-threatening disease	Renal or other organ-threatening disease; serum creatinine <500 µmol/l (5.6 mg/dl)	Renal or other vital organ failure; serum creatinine >500 µmol/l (5.6 mg/dl)	Progressive disease unresponsive to CS and CYC	Absence of disease features that pose immediate threats to either the patient's life or a critical individual organ (if hematuria, no red blood cell casts; serum creatinine <1.4 mg/dl, and no rise >25% above baseline level; if pulmonary involvement, must be circumscribed, with PO_2 >70 mm/Hg or O_2 saturation >92%; if pulmonary hemorrhage, must be nonprogressive; no gastrointestinal tract, eyes or central nervous system involvement)	Disease not classifiable as limited
Additional remark	Typically ANCA-negative	Constitutional symptoms present. ANCA-positive or negative	ANCA-positive	ANCA-positive	Refractory to standard therapy	Not severe	Organ- or life-threatening disease requiring CYC
Vasculitis involvement other than ENT and lung	No	Yes	Yes	Yes	Yes	Allowed but not required	Yes
Vital organ function threatened	No	No	Yes	Organ failure	Yes	No	Yes
Serum creatinine (µmol/l)	<120	<120	<500	>500 if renal involvement	All values	≤124, with/without microscopic hematuria but without red blood cell casts	All values

ANCA: Antineutrophil cytoplasmic antibody; CS: Corticosteroids; CYC: Cyclophosphamide; ENT: Ear, nose and throat; EULAR: European League Against Rheumatism; EUVAS: European Vasculitis Study Group; VCRC: Vasculitis Clinical Research Consortium; WGET: Wegener's Granulomatosis Etanercept Trial.
Adapted from the articles by Hellmich et al. [54] *on EULAR recommendations for conducting clinical studies and/or trials in ANCA-associated vasculitis, and Stone* et al. *on the WGET trial* [57,126].

Table 4. Prognostic five-factor score.

Five factor score	5-year survival rate (%)	Relative risk
0	88.1	0.62
1	74.1*	1.35
≥2	54.1‡	2.40

**p < 0.005 compared with patients with five-factor score = 0.*
‡p < 0.0001 compared with patients with five-factor score = 0.

More recently, the randomized NORAM trial [64] showed that, for newly diagnosed WG (n = 89) or MPA (n = 6) patients with early systemic forms, defined as those without organ- or life-threatening manifestations and with serum creatinine of 150 µmol/l or less, 15 mg/week of oral MTX progressively increased to 25 mg/week was not inferior to oral CYC at inducing remission at 6 months (89.8% achieved remission with MTX vs 93.5% with CYC; p = 0.04). However, it is possible that, because the remission-inducing agent was continued for only 12 months, the relapse rate at 18 months was higher for MTX recipients (69.5 vs 46.5% for the CYC group, with a median remission-to-relapse time of 13 and 15 months, respectively; p = 0.02), meaning that MTX recipients required higher cumulative CS doses to control their disease.

Hence, MTX can be used to treat WG patients like those with limited or early systemic forms, but it should be continued for more than 12 months and at a sufficient dose of 20–25 mg/week when tolerated, as stated in the EULAR recommendations (TABLE 2) [65]. Because the NORAM trial included only six MPA patients [64], it would seem unreasonable, in our opinion, to extend this conclusion to MPA patients with early systemic disease, as defined in that RCT. That small number of MPA data emphasizes that the need persists to determine more precisely whether or not MPA patients with a FFS of 0 and no organ- or life-threatening manifestations would benefit from systematic adjunction of an immunosuppressant that is less toxic than CYC, for example, AZA or MTX, to CS as first-line therapy. A trial is ongoing in France to try to determine the impact of AZA combined with CS as first-line therapy in such patients (CHUSPAN 2 trial; ClinicalTrials.gov number NCT00647166 [202,203]).

Maintenance therapy for Wegener's granulomatosis & microscopic polyangiitis

When WG is severe or generalized and for MPA patients with a FFS of 1 or higher, the first-line therapeutic regimen must include a combination of CS and a potent immunosuppressant, such as CYC, to induce remission, thereafter switching the latter to a less toxic drug for several months to maintain remission. Such staged strategies have been devised and proposed by several groups for years [59,66–68], and were further validated through RCTs and are now consensually considered the gold-standard therapy [69–71].

The CYCAZAREM (CYC vs AZA for the early remission–maintenance phase of vasculitis) trial demonstrated that AZA was as effective as continuing oral CYC for maintaining MPA and WG remissions [72]. The results of an open-label, prospective trial by Langford *et al.* on 31 WG patients also suggested that 20–25 mg/week of oral MTX was perhaps as effective as continued oral CYC for maintenance [69,73]. The results of some other retrospective or open-label studies also supported the possible use of MTX for maintenance, but emphasized that it was not able to lower the relapse rate below 30% 2 years after switching from induction to maintenance therapy [74].

Under the aegis of the French Vasculitis Study Group, we compared MTX and AZA as maintenance agents for 126 patients with WG or MPA who achieved remission using intravenous (IV) CYC and CS [75]. They received 12 months of maintenance with either AZA (2 mg/kg/day) or oral MTX at the starting dose of 0.3 mg/kg/week, then increased to a maximum and optimal dose of 25 mg/week. For patients weighing less than 80 kg, the MTX dose was planned to be rapidly increased within 2–4 weeks to 25 mg/week if tolerated. We concluded that the two drugs were equally effective

Box 2. Prognostic five-factor score; factor: add 1 point for each.

- Proteinuria >1 g/24 h
- Serum creatinine >140 µmol/l
- Specific gastrointestinal involvement
- Specific cardiomyopathy
- Specific CNS involvement

Devised based on the analysis of 342 patients with polyarteritis nodosa or Churg–Strauss syndrome [55]*, and subsequently also validated for microscopic polyangiitis patients* [127].

and that neither was significantly safer. With a mean follow-up of 29 months after remission, 36% of the AZA-groups patients and 33% of MTX recipients suffered a relapse (p = 0.71), mainly after maintenance-drug discontinuation. However, 56% of the MTX recipients suffered at least one adverse event compared with 46% of those taking AZA (p = 0.29), and 18% of the MTX recipients experienced a severe adverse event, defined as a WHO grade 3 or 4 event, compared with 8% of those given AZA (p = 0.11). Moreover, the only drug-related death occurred in the MTX arm and was due to pancytopenia immediately followed by sepsis in a 75-year-old man. The efficacy and safety differences were not statistically significant, but these findings might still highlight the potentially higher toxicity of MTX in vasculitis patients, most of whom are older than rheumatoid arthritis patients and have renal impairment.

Indeed, AZA, rather than MTX, has been evaluated in several international trials and is currently undergoing further trials, such as RAVE (rituximab for the treatment of WG and MPA; ClincialTrilas.gov number NCT00104299 [204]) or MAINRITSAN (maintenance of remission using rituximab in systemic antineutrophil cytoplasmic antibody-associated vasculitides; ClincialTrials.gov number NCT00748644 [205]), as the control drug for maintenance.

Notably, MTX was also compared with LFL, 30 mg/day, both given orally, for maintenance in 54 patients with generalized WG [76,77]. In that RCT, the overall relapse rates did not differ significantly (23.1% for the LFL patients vs 46.4% for the MTX recipients; p = 0.09), but the major relapse rate was higher for the MTX group (25 vs 3.8%; p = 0.037) within the first 6 months after starting maintenance, and engendered the premature termination of the trial. However, adverse events tended to occur more frequently with LFL (p = 0.09), especially hypertension, peripheral neuropathy or leukopenia, leading to its withdrawal for 19.2% of the patients (vs 0% of the MTX recipients). In addition, the initially low MTX dose (7.5 mg/week) and its slow increment, reaching 20 mg/week only after 2 months, might explain that somewhat higher rate of early relapses in MTX-treated patients.

Methotrexate for other vasculitides

The FFS can be applied at diagnosis to patients with PAN not related to hepatitis B virus infection or CSS to help adjust therapy based on the disease severity. PAN or CSS patients with one or more of the FFS manifestations should receive combined with an immunosuppressant, mainly CYC and not MTX, to obtain remission. However, MTX can be used thereafter to maintain remission of CSS and PAN, as for WG and MPA [65,71,78].

Conversely, PAN or CSS patients without any poor-prognosis factors do not require CYC and can be treated with CS alone. Thus, immunosuppressants can only be kept and prescribed for those patients who are dependent on taking over 5–10 mg/day of prednisone, have refractory disease and/or for CS-sparing in patients who suffer severe CS-related adverse events. CYC, AZA or possibly MTX can be used as second-line therapy in these latter patients, and the drug can be chosen according to disease severity [79,80]. However, the debate continues as to whether PAN or CSS patients with a FFS of 0, especially those with peripheral nervous system and/or cutaneous PAN [80–85], would benefit from the adjunction to CS of a drug that is less toxic than CYC – that is, AZA or MTX – as first-line therapy. The previously cited, randomized, controlled, double-blind CHUSPAN 2 trial is trying to address this issue using AZA. In an open-label study on 11 CSS patients with non-life-threatening manifestations, Metzler *et al.* demonstrated that the combination of CS and IV MTX at 0.3 mg/kg/week induced remission in eight patients but, when MTX was continued and given for remission maintenance, half of them relapsed after a median of 22 months (range: 8–16 months) postremission [78]. However, MTX achieved significant CS-sparing and caused little toxicity.

For Kawasaki disease, while prospective data are lacking, a few case reports suggested that MTX might be effective in patients with resistant or recurring disease, despite IV immunoglobulin therapy [86–88].

Combined immunosuppressive regimen including methotrexate

Combining MTX and AZA or MMF might be beneficial for some patients whose disease is refractory to one of these drugs prescribed alone, but not severe enough to require CYC. No trial testing such combinations for vasculitis patients has yet been undertaken but we, and others, have already successfully treated some patients with MTX and AZA or MMF, at somewhat lower doses (10–15 mg/week MTX and 1–1.5 mg/kg/day AZA or 1 g/day MMF). Several reports have been published on patients

with rheumatoid arthritis, Still's disease or inflammatory myopathies who have benefited from such combinations [69,89–95]. Studies are therefore clearly needed to further evaluate such combination strategies [96].

Conclusion

Methotrexate as first-line therapy, combined with CS, should be considered for newly diagnosed patients with GCA and, perhaps, TA when the disease is extensive or highly inflammatory. MTX also has a place in the treatment of refractory or CS-dependent GCA or TA and can therefore be used as a CS-sparing agent.

The CS and MTX combination can be prescribed as induction therapy for patients with limited forms of WG. As maintenance therapy, once remission has been achieved, the role of MTX in antineutrophil cytoplasmic antibody-related vasculitides has been now demonstrated by numerous studies. However, because vasculitis patients tend to be older and have more frequent renal impairment than those with rheumatoid arthritis, AZA is often preferred for maintenance, with MTX seen as an alternative for patients who do not tolerate AZA or have previously experienced relapse(s) under AZA.

Table 5. Practical guide for physicians prescribing methotrexate to treat systemic vasculitides.

Points to consider	Remarks
Dose	Standard dose range: 10–25 mg/week – GCA: 10–15 mg/week might be sufficient – TA: 15–25 mg/week is the optimal dose ANCA-associated vasculitides (induction for limited WG): start at 15 mg/week (EULAR recommendations) or 0.3 mg/kg/week, and try to increase to 20–25 mg/week over the next 1–2 months, if tolerated, for >12 months (optimal duration remains to be determined) ANCA-associated vasculitides (maintenance): 0.3 mg/kg/week and try to increase to 25 mg/week over the next 1–2 months, if tolerated, for ≥18 months – After remission induction with intravenous CYC: start MTX within 2–4 week after the last pulse – After remission induction with oral CYC: start MTX within the 2–3 week after the last dose
Route	Oral more convenient Inject subcutaneously or intramuscularly in the case of gastrointestinal intolerance of oral MTX, malabsorption or doubt regarding compliance
Precautions before starting treatment	Respect contraindications (see **Box 1**) and refer to updated pharmaceutical notices Rule out active infection Baseline testing: CBC, liver transaminases, serum creatinine, hepatitis B and C serologes, chest x-ray, tuberculine skin test Avoid MTX when GFR <30 ml/min, especially in the elderly Evaluation of alcohol consumption Discuss desire of pregnancy and means of contraception *MTHFR* polymorphisms might be associated with more frequent toxicity, but testing is not widely available
Monitoring	Check for clinical tolerance CBC, liver transaminases and serum creatinine should be tested Monitor every 2–4 weeks for 3 months following initiation or after increasing the dose, every 8–12 weeks for the next 3 months, and every 12 weeks thereafter Be aware of immunoallergic adverse events (acute interstitial pneumonitis, anaphylactic and hypersensitivity reactions) or liver fibrosis and/or cirrhosis Re-evaluate the need to continue MTX regularly
Associated measures	
Pneumocystis jiroveci prophylaxis	Avoid cotrimoxazole (at least, do not exceed 400/80 mg/day sulfamethoxazole/trimethoprim or, alternatively, 800/160 mg three times a week) Preferentially consider aerosolized pentamidine (300 mg every 3–4 weeks until 3 months after MTX discontinuation, when $CD4^+$ T lymphocytes ≤250/mm^3)
Folate supplementation	Dose of 1 mg/day folic acid (oral), except the day of MTX, or 5–7 mg 48 h after MTX Alternative: 5 mg folinic acid (oral) 48 h after MTX
Concomitant exposures to avoid	
Cotrimoxazole	Increases the risk of cytopenias and other MTX-related side effects
High-dose aspirin	Decreases renal clearance of MTX by 35–47%

ANCA: Antineutrophil cytoplasmic antibody; CBC: Complete blood count; CYC: Cyclophosphamide; EULAR: European League Against Rheumatism; GCA: Giant cell arteritis; GFR: Glomerular filtration rate; MTHFR: Methylenetetrahydrofolate reductase; MTX: Methotrexate; TA: Takayasu's arteritis; WG: Wegener's granulomatosis. Data from [25,34,65,75,128,129].

While treating rheumatoid arthritis patients with MTX, rheumatologists have gained considerable experience with its short- and long-term adverse effects, compared with newer biologics. However, a few nuances must be applied when giving MTX to vasculitis patients (Table 5). Notably, physicians must be aware that MTX should be prescribed for a sufficiently long duration at a sufficiently high and rapidly achieved dose. In addition, cotrimoxazole should preferably not be given concomitantly with MTX because of the risk of increasing its toxicity, even though cotrimoxazole has also been separately demonstrated to be associated with a lower WG relapse rate [97].

Future perspective

Over the last 10 years, the therapeutics of systemic vasculitides have considerably evolved from exclusive CYC- and/or CS-based regimens to new staged treatment approaches, using better tolerated and less toxic immunosuppressants with similar efficacy. However, relapse rates still exceed 30% at 2 years and newer agents and/or treatment strategies are imperatively needed to lower them.

The results of ongoing studies comparing MMF versus AZA (the EUVAS REMAIN trial; ClinicalTrials.gov number NCT00307645 [206]) or MTX (US trial; ClinicalTrials.gov number NCT00004567 [207]) as maintenance therapy for WG and/or MPA are pending. Outcomes of ongoing RCTs with the monoclonal anti-CD20 agent rituximab, as induction therapy in the RAVE trial (ClinicalTrials.gov number NCT00104299 [204]) or maintenance therapy in the MAINRITSAN study (ClinicalTrials.gov number NCT00748644 [205]), will also be of considerable interest. The findings of those studies might considerably change the treatment of systemic vasculitides as we know it [71].

Another area worthy of examination is to evaluate the benefit of synergistic combinations of MTX with other agents, like AZA or MMF, or even, possibly, rituximab or newer biologics under development or being investigated, like the humanized anti-CD20 ocrelizumab or abatacept. Pertinently, MTX partially inhibits xanthine oxidase, one of the enzymes involved in AZA metabolism and, simplistically, its clearance [28,73]. Thus, different combinations of these agents, at somewhat lower or adapted doses, could potentially be prescribed as alternatives to CYC for patients with grumbling WG or refractory and nonlife-threatening systemic vasculitis, with good tolerability. Indeed, through a greater effect on granulomatous inflammation, MTX might be used as a complementary drug, for example, with anti-CD20 therapy, which may exert, as hypothesized in some reports, a

Executive summary

Indications of methotrexate for systemic vasculitides

- Giant cell arteritis
  - Consider for every newly diagnosed patient, especially those at risk for corticosteroid (CS)-related side effects.
  - Consider for refractory or relapsing disease, or patients who develop CS-related side effects.
- Takayasu's arteritis
  - Consider for refractory or relapsing disease, or patients who develop CS-related side effects.
  - May be used as first-line therapy with CS when disease is extensive or striking inflammation parameters.
- Wegener's granulomatosis
  - Induction therapy with CS for limited, early systemic, nonsevere forms.
  - Maintenance therapy, after induction of remission with cyclophosphamide (CYC), for severe or generalized forms, as an alternative to azathioprine.
- Microscopic polyangiitis
  - Maintenance therapy, after obtaining remission with CYC, for severe forms, as an alternative to azathioprine.
- Other systemic vasculitides
  - Lack of prospective evidence for clear recommendations.
  - Can be used for maintenance after achieving remission of Churg–Strauss syndrome or polyarteritis nodosa (not related to hepatitis B virus infection) for patients who required induction with CYC.

Methotrexate dosing

- Methotrexate must be prescribed for a sufficiently long duration and at an adequate dose to maximize its efficacy and prevent short- and long-term relapses.

Adverse effects of methotrexate

- Methotrexate has a relatively good safety profile, but close monitoring during follow-up is necessary to detect its potential hematologic, pulmonary and/or liver toxicity(ies).
- Elderly vasculitis patients or those with impaired renal function may be more prone to certain side effects because of the accumulation of the drug and its metabolites.

more rapid and possibly preferential, although not exclusive, effect on systemic vasculitis manifestations [98–101].

While awaiting the results of the aforementioned or hopefully forthcoming studies, experience carries the day and old friends, such as AZA or MTX, are the best.

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1. Which of the following adverse effects is most frequent among users of methotrexate with rheumatic diseases?

- ☐ **A** Nausea and vomiting
- ☐ **B** Elevated transaminases
- ☐ **C** Cough and exertional dyspnea
- ☐ **D** Malaise and fatigue

2. Which of the following best describes laboratory tests recommended in the first 3 months of methotrexate therapy?

- ☐ **A** Complete blood count, creatinine, transaminase, and albumin levels every 2–4 weeks
- ☐ **B** Transaminases, bilirubin, electrolytes, and urinalysis every 2–3 weeks
- ☐ **C** Complete blood count, bilirubin, transaminases, and uric acid every 1–2 weeks
- ☐ **D** Creatinine, transaminases, electrolytes, urinalysis, and chest x-ray every 4–6 weeks

3. Which of the following is most likely to be a large-vessel arteritis?

- ☐ **A** Wegener's granulomatosis
- ☐ **B** Takayasu's arteritis
- ☐ **C** Churg–Strauss syndrome
- ☐ **D** Kawasaki disease

4. Which of the following vasculitides has the least evidence supporting use of methotrexate with or without corticosteroids as first-line therapy?

- ☐ **A** Giant cell arteritis
- ☐ **B** Wegener's granulomatosis
- ☐ **C** Takayasu's arteritis
- ☐ **D** Polyarteritis nodosa