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Vasculitis therapy refines vasculitis mechanistic classification

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Ustekinumab
Abatacept
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ABSTRACT

The primary vasculitides constitute a heterogeneous group of immune mediated diseases of incompletely understood pathogenesis currently classified by the size of blood vessels affected (Chapel Hill classification). In recent years, several drugs with well-characterized immunological targets have been tested in clinical trials in large vessel vasculitis and small vessel vasculitis. Such trials provide "reverse translational" or bedside to bench information about underlying pathogenic mechanisms. Therefore, the aim of this systematic literature review was to examine the evidence base for a more refined mechanistic immunological classification of vasculitis. A total of 40 studies (20 randomized controlled trials (RCTs), 16 prospective studies, 1 retrospective cohort study and 3 case series) were included for full qualitative assessment. RCTs concerning biologic therapy for large vessel vasculitis mainly supports interleukin 6 receptor inhibition (tocilizumab). RCTs concerning biologic therapy for granulomatosis with polyangiitis and microscopic polyangiitis mainly support anti-CD20 treatment (rituximab) and complement inhibition with a small molecule C5a receptor antagonist (avacopan) is an emerging treatment option. The biologic treatment of eosinophilic granulomatosis with polyangiitis is centered around interleukin 5 inhibition (mepolizumab). Studies on tumor necrosis factor alpha inhibition (adalimumab, infliximab, and etanercept) showed negative results in giant cell arteritis but some effect in Takayasu arteritis. Taken together, clinical studies with cytokine and cell specific drugs are dissecting the heterogeneous immunopathogenic mechanisms of vasculitis and support a mechanistic immunological classification. Especially, cytokine antagonism is pointing towards immunological distinctions between eosinophilic granulomatosis with polyangiitis and granulomatosis with polyangiitis/microscopic polyangiitis and differences between giant cell arteritis and Takayasu arteritis.

List of abbreviations

Disease	
AAV	ANCA-associated vasculitis
ANCA	Antineutrophil cytoplasmic antibody
EGPA	Eosinophilic granulomatosis with polyangiitis
GCA	Giant cell arteritis
GPA	Granulomatosis with polyangiitis
LVV	Large vessel vasculitis

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MPA	Microscopic polyangiitis
SVV	Small vessel vasculitis
TA	Takayasu arteritis
Other abbreviations	
APC	Antigen Presenting Cell
BAFF	B cell Activating Factor
CR	Complete Remission
DMARD	Disease Modifying Anti-Rheumatic Drug

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(*continued*)

IL	Interleukin
MPO	Myeloperoxidase
PBMC	Peripheral Blood Mononuclear Cells
PR	Partial Remission
PR3	Proteinase 3
SR	Sustained Remission
Th	T-Helper
TNFα	Tumor Necrosis Factor Alpha

1. Introduction

Vasculitis is a generalized term for a heterogeneous group of diseases characterized by inflammation of blood vessels. Numerous classifications of the primary vasculitides have been proposed based on their involvement of specific groups of blood vessels, tropism for certain organ systems and characteristic pathologic features [1]. The most commonly used nomenclature was proposed by the Chapel Hill Consensus conference and is based on the size of vessels affected [2]. However, efforts are still ongoing to improve classification criteria for the primary systemic vasculitides [3].

Large vessel vasculitis (LVV) includes giant cell arteritis (GCA) and Takayasu arteritis (TA), and present as granulomatous inflammation involving the large arteries. Small vessel vasculitis (SVV) is classified into antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and vasculitis associated with immune complex deposition. AAV is a necrotizing vasculitis involving small vessels and is associated with ANCA specific for proteinase 3 (PR3) or myeloperoxidase (MPO) [4,5]. AAV include granulomatosis with polyangiitis (GPA, formerly Wegener's Granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss Syndrome). Clinical studies on AAV usually only include either GPA and MPA patients or EGPA patients, although EGPA is part of the AVV classification.

The use of glucocorticoids and the conventional synthetic class of disease modifying anti-rheumatic drugs (DMARDs) such as cyclophosphamide, methotrexate, mycophenolate mofetil and azathioprine have been central to the management of vasculitis with these drugs having broad impact of both innate and adaptive immunity or predominantly on lymphocyte function [1,6]. However, the exact mechanism of action for these compounds is not fully understood. In contrast, highly specific cytokine and cell targeted drugs have been successfully implemented in rheumatology and other settings and are now emerging in the vasculitis arena. For example, inhibitors of TNFα and the IL-6 receptor were developed for the treatment of rheumatoid arthritis, antibodies targeting CD20 were developed for the treatment of B cell lymphoma and inhibitors of IL-5 were developed for the treatment of asthma, with these targeted therapies subsequently being assessed in clinical trials in vasculitis.

The clinical efficacy (or lack of efficacy) of drugs with well-characterized immunological targets generate imperative "reverse translational" or bedside to bench information about immune pathogenesis that was not discernible with prior pan-immune system or pan-lymphocyte inhibition. Fig. 1 illustrates the immunology behind the drugs described in this review to allow reverse translation of their clinical use. CD80/86 is a membrane molecule expressed by antigen presenting cells providing co-stimulation to T cells. IL-6, IL-12 and IL-23 are major macrophage cytokines with importance for T-cell subset differentiation. TNFα is another macrophage cytokine also secreted by Th1 cells and IL-17 is an important Th17 effector cytokine (Fig. 1A). CD20 is a membrane molecule expressed by B cells and BAFF is a cytokine involved in differentiation of B cells into plasma cells (Fig. 1B). C5a is a complement split product and IL-1β is a major effector cytokine from neutrophil granulocytes (Fig. 1C). Finally, IL-5 is secreted by many cells

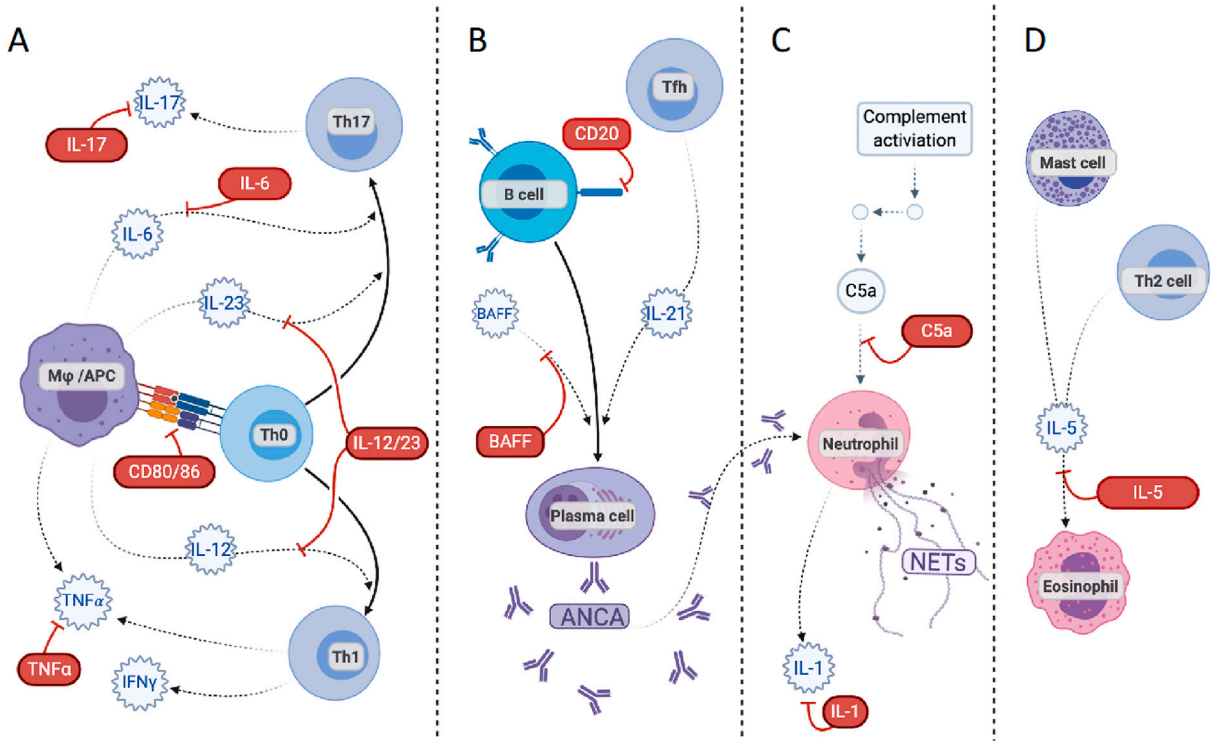

Fig. 1. Overview of the immunologic pathways targeted by the drugs described in this review. A) Illustration of important macrophage/APC interactions including Th cell differentiation into Th1 cells and Th17 cells. B) Illustration of B cells differentiating into autoantibody-producing plasma cells. C) Illustration of complement activation and neutrophil stimulation. D) Illustration of IL-5 stimulation of eosinophilic granulocytes. Th; T helper. IL; interleukin. Mϕ; macrophage. APC; antigen presenting cell. TNF; tumor necrosis factor. IFN; interferon. CD; cluster of differentiation. BAFF; B cell-activating factor. ANCA; anti-neutrophil cytoplasmic antibody. NETs; neutrophil extracellular traps.

including Th2 cells and activates eosinophil granulocytes (Fig. 1D).

Here, we provide a bedside to bench analysis of current evidence on the therapeutic efficacy of biologic DMARDs and small molecules for the LVVs GCA and TA and the ANCA-associated SVVs. This was achieved by a systematic literature review of vasculitis therapy through the lens of how it could inform an improved mechanistic immunological classification of vasculitis.

2. Materials and methods

We conducted a systematic review to examine the evidence base for a mechanistic immunological classification of vasculitis in accordance with the PRISMA statement [7]. To be able to generate bedside to bench information on cytokine or cell specific therapies, only vasculitis diagnosis with at least one biological drug with a U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMA) approval were included. We did not include diseases with only an approved targeted synthetic DMARD. This is because immunological translation of the synthetic targeted DMARDs targeting PDE4 and Janus kinase (JAK) signaling is more complex to translate into immunological understanding given combinatorial cytokine and cell inhibition mechanisms. Therefore, Behcet's disease was not included even though the targeted synthetic DMARD apremilast is approved for some manifestations of this disease. The included diseases were the LVVs GCA and TA and the AAVs GPA, MPA, and EGPA.

2.1. Search strategy

A systematic literature review on the use of biologic DMARDs and avacopan for the management of GCA, TA, GPA, MPA, and EGPA was performed on PubMed. The search term was a combination of <disease terms> AND <drug terms>. See supplementary S1–S2 for a full list of disease and drug terms. The search included records from database inception (the earliest study is from 2001) to August 20th, 2020. Records were filtered using the filter function on PubMed. Filters used were 'clinical trials (+phase I/II/III/IV)', 'case reports', 'controlled clinical trial', 'observational studies' and 'randomized controlled trials'. Only English literature was included. A hand-search was done on reference lists of relevant reviews to identify additional studies. A search on clinicaltrials.gov for ongoing trials on GCA, TA, GPA, MPA, and EGPA was performed. Recruiting, active and completed (but unpublished) trials evaluating biologic DMARD treatment of these vasculitis subtypes were included.

2.2. Study selection

Records were screened for relevance according to title and abstract. Inclusion criteria were randomized-controlled trials (RCTs), prospective and retrospective cohort studies and case series concerning the treatment of LVV and AAV patients with the included DMARDs. Studies were required to report at least one of the following outcomes: remission, relapse or glucocorticoid usage. No criteria for length of follow-up were set. Case series were only included if they reported $\geq$3 patients. For the drug and disease combinations that are FDA approved, only RCTs were included for full qualitative synthesis. Retrospective studies and case series were excluded from full qualitative synthesis if any RCT or prospective cohort trial existed on the disease and drug combination. The reason for this exclusion was that this article does not aim to provide a complete evidence overview, but rather to investigate the evidence base of targeting specific immunological pathways. Study selection was done by two reviewers (CKT and MB). Conflicts were resolved by a third reviewer (TWK).

2.3. Data extraction and quality assessment

Data collected included patient demographics (number of patients, age, sex, newly diagnosed or relapsing/refractory at enrollment), length of follow-up, DMARDs used with dose and frequency, concomitant therapy, primary end point, remission and relapse rates and glucocorticoid usage (mean usage, cumulative usage or number of patients under a certain daily usage threshold at end of follow-up).

The Cochrane Risk of Bias Tool from 2011 was used to assess internal validity in RCTs across seven domains (sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other sources of bias) [8]. Each RCT is presented as low or high risk of bias. If one domain had a high risk of bias, the study was rated as having a high risk of bias. For prospective cohort studies a modified Newcastle-Ottawa Scale was used that assessed three domains (whether patients were enrolled consecutively or hand-picked, whether outcome data was complete (>90%) and whether a standardized approach to outcome assessment was used) [9]. Each domain would award a star, and studies were rated as being poor, fair or good regarding internal validity and risk of bias with 1, 2 and 3 stars respectively. Retrospective studies and case series were not assessed for quality. Protocols of trials were not searched for information sequence generation, allocation concealment, pre-specified outcomes or blinding, and no authors were contacted regarding missing data. Data extraction and qualitative assessment was done by two reviewers (CKT and MB).

3. Results

3.1. Studies included

The search in PubMed identified 589 articles. Seven additional studies not identified in the PubMed search were included from reference lists [10–16], including 5 prospective cohort studies [10,11,13,15,16], 1 retrospective cohort study [14] and 1 case series [12]. See supplementary S3 for the full selection process. A total of 40 studies underwent full evaluation. Seven articles contained data on overlapping study populations (RITUXVAS trial [17,18], RAVE trial [19–21] and MAINRITSAN trial [22,23]), but were all included.

The qualitative synthesis included 20 RCTs [17–36], 16 prospective cohort studies [10,11,13,15,16,37–47], 1 retrospective cohort study [14] and 3 case series [12,48,49]. Patients in RCTs were treated with: avacopan [35], mepolizumab [34], tocilizumab [30,32,33], infliximab [25,26], etanercept [24,29], adalimumab [31], abatacept [27,28], rituximab [17–23,25] and belimumab [36]. Patients in prospective cohort studies were treated with: tocilizumab [15,41,46], infliximab [39,42–44,47], etanercept [37,38], adalimumab [45], ustekinumab [10,11,16], abatacept [13] and rituximab [40]. Patients in the retrospective cohort study were treated with rituximab [14]. Patients in case series were treated with anakinra [48], etanercept [49] and ustekinumab [12].

3.2. Quality assessment of included studies

Seven RCTs were assessed as having a low risk of bias [19,26,30,32,34–36], while 13 were assessed as having a high risk of bias [17,18,20–25,27–29,31,33]. Detailed assessment of risk of bias can be found in supplementary S4 [50]. For prospective cohort studies, a single study was reported as having good internal validity [43]. Twelve studies were report as having fair internal validity, as they did not report whether patients were consecutively enrolled [10,11,13,37–42,44–47]. Two studies were rated as fair due to loss of follow-up [15,16].

3.3. Evidence synthesis

Results from RCTs and prospective cohort studies are summarized in Table 1. Detailed assessment of each study can be found in supplementary S5–9, including patient demographics, length of follow-up, DMARDs used with dose and frequency, concomitant therapy, primary

Table 1
Results from RCTs and prospective cohort studies evaluating treatment of large- and small vessel vasculitides with the DMARDs included in this review. Detailed assessment of each study can be found in supplementary S5–S9.

		Targets of the DMARDs									
		IL-6	TNFα	IL-12/23	IL-1	IL-17	CD80/86	CD20	BAFF	C5a	IL-5
LVV	GCA										
	TA										
SVV	GPA										
	MPA										
	EGPA										
		US FDA or EMA Approval Primary end point met in a RCT Uncontrolled trial supporting clinical efficacy				Primary end point not met in a RCT or controlled prospective study Retrospective studies, case series or not studied					

LVV; large vessel vasculitis. GCA; giant cell arteritis. TA; Takayasu arteritis. SVV; small vessel vasculitis. GPA; granulomatosis with polyangiitis. MPA; microscopic polyangiitis. EGPA; eosinophilic granulomatosis with polyangiitis. IL; interleukin. TNF; tumor necrosis factor. CD; cluster of differentiation. BAFF; B cell-activating factor. FDA; Food and Drug Administration. EMA; European Medicines Agency.

end point and the following outcomes: remission and relapse rates and glucocorticoid usage (mean usage, cumulative usage or number of patients under a certain daily usage threshold at end of follow-up).

3.3.1. IL-6 receptor inhibition

The IL-6R antagonist tocilizumab is the most studied biologic drug in LVV. In a RCT by Stone et al. 251 newly diagnosed and relapsing GCA patients were randomized in 4 treatment arms [32]. The primary endpoint of sustained remission at week 52 was met in a significantly larger percentage of patients in tocilizumab and glucocorticoid treatment groups (both with 26-week glucocorticoid taper) compared to the placebo and glucocorticoid treatment groups (26- and 52-week glucocorticoid taper). Rates of relapse and cumulative glucocorticoid dose were also significantly lower. The efficacy of tocilizumab in GCA is supported in a smaller RCT by Villiger et al., where 30 newly diagnosed and relapsing patients were randomized to receive either tocilizumab and glucocorticoids or placebo and glucocorticoids [33]. The tocilizumab group was significantly better in both remission at week 12 (primary endpoint), relapse-free survival and cumulative glucocorticoid usage at week 52.

With respect to TA, Nakaoka et al. [30] evaluated the efficacy of tocilizumab for the maintenance of glucocorticoid induced remission in 36 patients with relapsing disease. The study did not meet its primary endpoint of time to relapse. However, sustained remission was significantly increased in the tocilizumab group and a decrease in relapses was observed when compared with placebo. Efficacy of tocilizumab in TA is supported in two prospective cohort studies. Kong et al. [46] compared treatment effects of tocilizumab and cyclophosphamide and reported a higher degree of decrease in biochemical parameters in the tocilizumab group. Zhou et al. [15] reported improvements in biochemical and radiological parameters in 13 patients treated with tocilizumab plus glucocorticoid.

A single prospective cohort study evaluated the efficacy of tocilizumab in 7 MPA patients [41]. Complete or partial remission was observed in six out of seven patients one month after induction. No studies have been conducted with IL-6 inhibition in patients with GPA or EGPA.

3.3.2. TNF inhibition

RCTs that evaluated efficacy of anti-TNFα and glucocorticoid in newly diagnosed GCA patients showed negative results. RCTs evaluating infliximab [26] and adalimumab [31] failed to meet their primary endpoints of relapse-free remission. The etanercept RCT [29] was not significant in meeting its primary endpoint of corticosteroid withdrawal. A prospective cohort study by Hoffman et al. [37] evaluated infliximab and etanercept as adjunct therapy with glucocorticoid in 15 patients with relapsing TA patients with promising results. A more recent study by Park et al. [47] evaluating infliximab biosimilar CT-P13 in TA patients had similar positive results with improvements in biochemical parameters and a significant reduction in inflammation based on positron emission tomography scans.

The RCT Wegener's Granulomatosis Etanercept Trial (WGET) evaluated TNFα-inhibitor etanercept as a treatment option for 181 newly diagnosed and relapsing GPA patients, and concluded that etanercept was not effective for the maintenance of remission [24]. Supporting this, a smaller RCT comparing infliximab and rituximab concluded that TNFα inhibition was inferior to B cell depletion in obtaining and maintaining remission in relapsing patients [25]. A prospective cohort study showed that combined infliximab and glucocorticoid therapy induced prompt symptomatic responses in 7 relapsing GPA patients, but follow-up was short [42]. Three prospective cohort studies evaluating TNFα blockade in AAV showed contradictory results [43–45]. TNFα inhibition has yet to be evaluated in EGPA patients.

3.3.3. IL-12/23 inhibition

Conway et al. evaluated the efficacy of IL-12/23 inhibitor ustekinumab and glucocorticoid for the treatment of relapsing GCA patients in two prospective cohort studies [10,11]. Patients were treated with ustekinumab and no relapses were observed during follow-up after remission was induced in both studies. Mean glucocorticoid at end point was significantly reduced. Contrasting these results, a study by Matza et al. [16] evaluating ustekinumab for new-onset and relapsing GCA patients was closed prematurely due to a high rate of treatment failure among the enrolled patients. IL-12/23 inhibition has not been studied in TA, GPA, MPA, or EGPA.

3.3.4. IL-1 inhibition

Efficacy of IL-1 blockade with anakinra as a treatment option for GCA was evaluated in a case series with 3 relapsing patients [48]. It was found to induce remission and have a steroid sparing effect in two of those 3 patients. No studies were found testing IL-1 inhibition in TA, GPA, MPA, or EGPA.

3.3.5. IL-17 inhibition

No studies on IL-17 inhibition were included in this SLR.

3.3.6. CD80/86 inhibition

Langford et al. evaluated the role of CD80/86 blockade with abatacept in newly diagnosed and relapsing GCA and TA patients in two RCTs [27,28]. Patients were initially treated with abatacept and glucocorticoid, and at 12 weeks randomized to continue treatment with either abatacept or placebo. Increased remission rate (significance was achieved with $p = 0.049$) and a decreased rate of relapse were observed in the abatacept group in the GCA trial, but no significant difference was observed between treatment arms in the TA trial. A prospective cohort study evaluated CD80/86 blockade with abatacept for 20 non-severe, relapsing GPA patients [13]. Abatacept was associated with a high frequency of disease remission and glucocorticoid discontinuation. CD80/86 blockade has not been investigated in MPA or EGPA.

3.3.7. Anti-CD20

Anti-CD20 monoclonal antibody rituximab is the biologic treatment used in most studies of patients with AAV (GPA and MPA). The RAVE RCT evaluated newly diagnosed and relapsing patients and found that rituximab and glucocorticoid met the criterion for non-inferiority concerning remission when compared to the cyclophosphamide/azathioprine and glucocorticoid control group [20]. The rituximab-based regimen was more efficacious for inducing remission of relapsing disease. The extended follow-up reported similar results [19]. A post-hoc analysis evaluating patients from the RAVE RCT concluded that patients with AAV and renal involvement respond similarly to remission induction with rituximab or cyclophosphamide [21]. The RITUXVAS RCT support the efficacy of rituximab treatment for AAV with renal involvement (mean GFR was 18 ml/min/1.73 m^2 body-surface area) in newly diagnosed patients [17]. The study randomized 44 patients to either a rituximab and glucocorticoid (with two intravenous cyclophosphamide pulses) or cyclophosphamide/azathioprine and glucocorticoid. The rituximab-based regimen was not superior, but sustained remission rates were high in both groups. The 24-month extended study supported these results long-term [18]. The more recent MAINRITSAN RCT randomized 115 newly diagnosed and relapsing patients to receive either rituximab and glucocorticoid or azathioprine and glucocorticoid for maintenance of remission [22]. More patients had sustained remission at month 28 with rituximab than with azathioprine. The extended follow-up even showed that these results persisted after 60 months of follow-up [23]. The RAVE, RITUXVAS and MAINRITSAN RCTs did not included EGPA patients, and evidence on clinical efficacy of rituximab for EGPA patients is currently restricted to low-evidence studies. An open-label prospective cohort study found rituximab successful in controlling EGPA renal disease activity, but only three patients were enrolled [40]. No studies have been reported evaluating anti-CD20 treatment for GCA and TA patients.

3.3.8. BAFF inhibition

A RCT evaluated the efficacy of the BAFF-inhibitor belimumab as adjunct therapy for maintenance of remission in newly diagnosed and relapsing AAV patients [36]. A total of 104 patients with induced remission were randomized to receive belimumab or placebo along with azathioprine and glucocorticoid for maintenance of remission. A decreased rate of relapse in the belimumab treatment group compared to the control group was not demonstrable. No studies were found on BAFF inhibition in GCA, TA, or EGPA.

3.3.9. C5a inhibition

The C5a receptor inhibitor avacopan was evaluated in a RCT as a potential replacement for glucocorticoid in newly diagnosed and relapsing AAV patients [35]. Patients were receiving either cyclophosphamide/azathioprine or rituximab therapy concomitantly with avacopan or glucocorticoid. Avacopan met the criteria for non-inferiority, and the study concluded it to be effective as a replacement for glucocorticoid therapy. C5a inhibition has not been studied in GCA, TA, or EGPA.

3.3.10. IL-5 inhibition

The efficacy of IL-5 blockade with mepolizumab for the treatment of EGPA was evaluated in a RCT by Wechsler et al. [34]. 136 patients with relapsing or refractory EGPA were randomized to either mepolizumab or placebo. Mepolizumab treatment led to significantly more accrued weeks of remission, lower annualized relapse rates and lower rates of glucocorticoid. IL-5 inhibition has not been studied in GC, TA, GPA, or MPA.

3.4. Ongoing trials

A detailed overview on current ongoing clinical trials can be found in supplementary S10, including interventions, number of patients, NCT-number and current trial status. Table 2 gives a summary of the identified trials.

4. Discussion

We undertook a SLR of 40 studies employing targeted immunotherapy for LVV and SVV with the aim of integrating these findings with known immunopathological and immunogenetic features of vasculitis to offer an improved "bedside to bench" model towards vasculitis classification. Our findings in the context of disease pathology further validate, confirm, or point towards likely differences in vasculitis within involved vascular territories.

Increased levels of IL-6 have been reported in both TA and GCA patients but IL-6R blockade has proven efficacy in GCA but still needs further studies in TA [51–53]. Genetic studies have found an association with HLA-DR4 in GCA patients and HLA-B52 in TA patients pointing to predominant MHC-II and MHC-I immunopathogenic mechanisms respectively [54–56]. It is noteworthy that anti-IL-6 therapy also lacks efficacy in other MHC-I associated conditions including ankylosing spondylitis and psoriasis. Like TA, these other MHC-I associated disorders show response to anti-TNF therapy [57,58]. Supporting this, a significant higher expression of TNFα (Th1 or NK-cell produced) has been shown in TA compared with GCA [52,59]. Conversely, TNF inhibition failed in GCA. Taken together, current evidence points towards a strong role of IL-6 within especially GCA while TA is more associated with TNFα.

B cell depletion with monoclonal anti-CD20 antibody rituximab has proven to be an effective treatment option for both newly diagnosed, relapsing and refractory GPA and MPA, highlighting the importance of adaptive immunity within AAV. The presence of autoantibodies in a wide range of non-vasculitis autoimmune diseases and rituximab responsiveness is well recognized. Although AAV is characterized by the presence of circulating antibodies, ANCA-negative cases are well recognized [4,60]. Despite the EGPA spectrum of disease shows similar vascular territory inflammation and autoantibody profiling as GPA and MPA, current literature on B cell depletion therapy in EGPA only includes case reports, retrospective studies and a single prospective cohort study. Recent data suggests that ANCA positive EGPA patients tended to respond better to rituximab than ANCA negative patients [61]. EGPA is characterized by a more prominent eosinophilic inflammation and IL-5 blockade has been shown to lead to disease improvements in EGPA [34,62]. While the exact immunopathogenesis of EGPA remains to be defined and refined to ANCA positive and negative EGPA, periods of active disease are characterized by large amounts of IL-5 secreted by Th1 and Th17, leading to eosinophil activation [63].

Inhibition of C5aR with avacopan has shown clinical efficacy in GPA and MPA which is entirely in keeping with classical complement pathway activation given the autoantibody associations. Further, the effect of C5aR inhibition in GPA and MPA is also in keeping with complement activation as part of intravascular innate immunity in the walls of smaller vessels and capillaries in vasculitis in general. Together with autoantibody deposition and other mechanisms, complement triggers exaggerated vascular immune responses and amplification of adaptive immune tissue damage. Current evidence also suggests a central role of the alternative complement pathway in AAV [64,65]. C5a activates neutrophils via C5aR binding leading to the release of neutrophil extracellular traps (NETs) [66,67].

CD80/86 blockade showed clinical promise in GCA patients but was not associated with any clinical effect in TA [27,28]. Interactions between antigen presenting cells and T cells through co-stimulatory receptors have been substantiated in experimental models of LVV [68–70] and the MHC class II genetics of GCA also points towards help T cell responses. Experimental studies also support the role of antigens in LVV [70–72]. Taken together, this suggests a T cell therapy target in especially GCA. At this point a single prospective cohort study evaluating CD80/86 blockade in GPA patients showed promising clinical results

Table 2
Overview of current ongoing clinical trials on the included DMARDs treatment of large- and small vessel vasculitides. Detailed overview can be found in supplementary S10.

		Targets of the DMARDs									
		IL-6	TNFα	IL-12/23	IL-1	IL-17	CD80/86	CD20	BAFF	C5a	IL-5
LVV	GCA										
	TA										
SVV	GPA										
	MPA										
	EGPA										
		Phase III/IV trials				Phase II trials					

LVV; large vessel vasculitis. GCA; giant cell arteritis. TA; Takayasu arteritis. SVV; small vessel vasculitis. GPA; granulomatosis with polyangiitis. MPA; microscopic polyangiitis. EGPA; eosinophilic granulomatosis with polyangiitis. IL; interleukin. TNF; tumor necrosis factor. CD; cluster of differentiation. BAFF; B cell-activating factor.

[13].

Two prospective studies supported clinical efficacy of IL-12/23 inhibition in GCA, however one prospective study did not support this treatment approach. The p40 SNP genetic association with GCA supports involvement of Th1 and Th17 pathways in this disease [55]. Currently, only an anecdotal case series with positive results evaluates ustekinumab as a treatment option in relapsing TA patients [12]. Ulcerative colitis is frequently found in TA patients, suggesting common pathways between TA and inflammatory bowel diseases. This is interesting because ustekinumab is widely used for patients with inflammatory bowel disease [73]. An in vitro study showed that both Th1 and Th17 cytokines were significantly enhanced in peripheral blood mononuclear cells of GCA patients, with IL-23 production (Th17) being most prominent [74]. In contrast, peripheral blood mononuclear cells from TA patients expressed significantly more IL-12 (Th1 and NK-cells) compared with healthy controls, but this was not observed for IL-23 (Th17 cells) [75]. These findings suggest that the Th1 pathway may be more important in TA, whereas the Th17 pathway may be more involved in GCA.

Although elevated levels of BAFF, have been observed in AAV patients [36,76], anti-BAFF therapy as an adjunct remission maintenance strategy to reduce the number of circulating B cells differentiating into plasma cells did not provide additional clinical benefits. The discrepancy between the effectiveness of B cell depleting treatment and BAFF inhibition may be that B cells have immunogenic functions (antigen presenting or cytokine production) in AAV besides production of autoantibodies.

IL-1, which is mainly produced by myeloid cells, has also been shown to be elevated in GCA patients [77,78]. IL-1 blockade with anakinra has been commissioned as a treatment option for fever syndromes and Adult

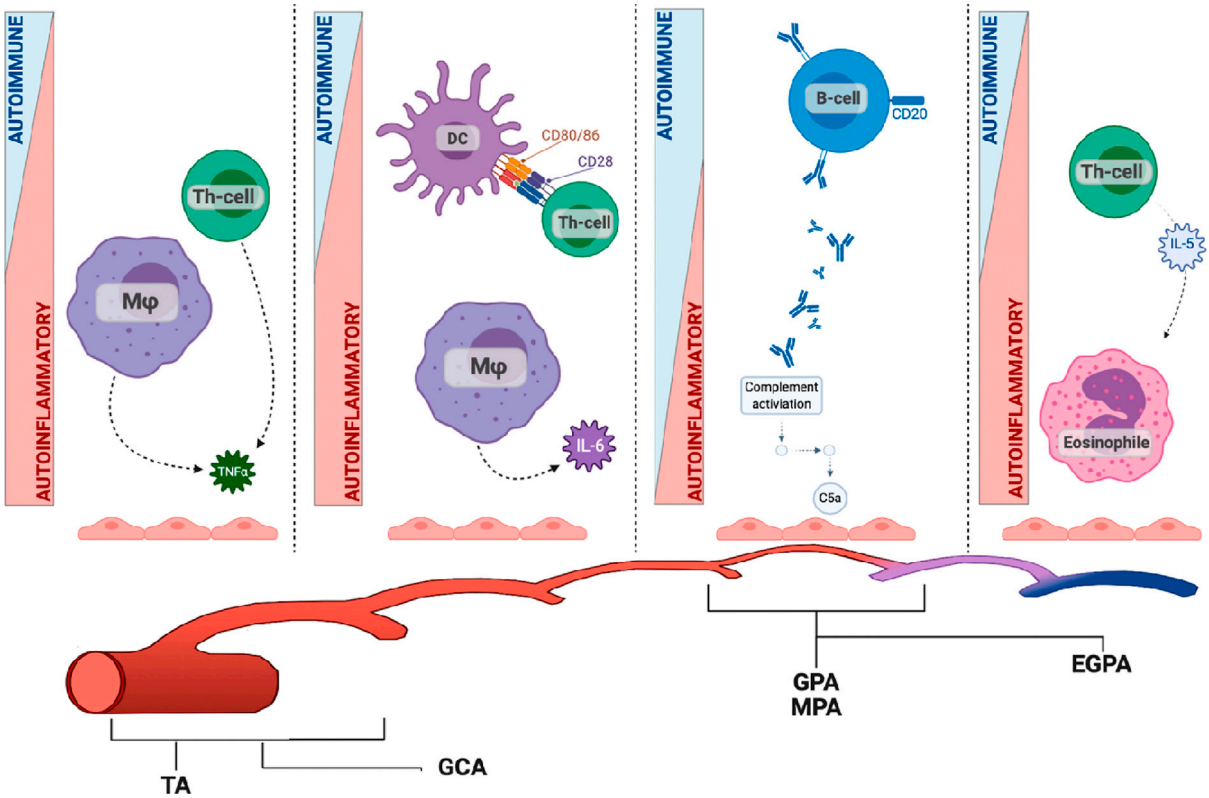

Fig. 2. Proposed mechanistic immunological classification of large and small vessel vasculitides based on reviewed evidence. The top part of the figure presents central immune cells within the pathology of vasculitis subtypes and an estimated weighing of autoinflammatory-autoimmune disease mechanisms. The bottom part represents the current Chapel Hill classification of vasculitides according to vessel size. The main difference is the separation of TA from GCA and EGPA from GPA/MPA. GCA; giant cell arteritis. TA; Takayasu arteritis. GPA; granulomatosis with polyangiitis. MPA; microscopic polyangiitis. EGPA; eosinophilic granulomatosis with polyangiitis. Th; T helper. IL; interleukin. Mϕ; macrophage. TNF; tumor necrosis factor. DC; dendritic cell. CD; cluster of differentiation. NETs; neutrophil extracellular traps.

Onset Still's disease [79,80]. Around 30–60% of GCA patients present with systemic symptoms such as low-grade fever [81]. However, at this point evidence from clinical use of IL-1 inhibition in GCA is limited to a single case series.

Our bedside to bench SLR confirms different biologic treatment approaches to LVV and SVV and supports further immunological heterogeneity within vasculitis. Based on this, it is possible to juxtapose these therapy differences onto the traditional model of vasculitis based on vessel size to refine disease mechanisms (Fig. 2), which illustrates the most important immune interactions along an autoimmune-autoinflammatory (or innate immunity) continuum [82] that also incorporates vessel size distribution for GCA, TA, GPA, MPA, and EGPA.

In conclusion, an immunology-based classification of vasculitis is in line with the anatomical-based Chapel Hill classification, with LVV having a major autoinflammatory or innate immune effector phase and the SVVs included in this review being primarily autoimmune diseases with variable interactions between both arms in determining the ultimate outcomes. However, within the SVV, especially ANCA negative EGPA seems to be immunologically very different from GPA/MPA. Further, the LVV subgroups with their radically different immunogenetic associations but commonality of histology and implied T-cell immunogenetics appear to differ in the role of IL-6 in GCA and TNF in TA, but this is preliminary, and more work is needed. Therefore, in an immunology-based classification based on current evidence, it would make sense to separate EGPA from GPA/MPA and to some extent TA from GCA.

Authors' contributions

CKT and TWK designed the project. CKT and MB performed the literature search, extracted data and evaluated quality of included studies. CKT made the first draft of the manuscript. All authors helped assess methodological quality of included studies and interpret study results. All authors critically reviewed the manuscript and approved the final version. MB made the graphical work for Figs. 1 and 2.

Ethics approval and consent to participate

Not applicable.

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Availability of data and material

Not applicable.

CRediT authorship contribution statement

Christopher Kirkegaard Torp: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing - original draft, Writing - review & editing. **Mads Brüner:** Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing - review & editing. **Kresten Krarup Keller:** Investigation, Methodology, Supervision, Validation, Writing - review & editing. **Elisabeth Brouwer:** Investigation, Methodology, Supervision, Validation, Writing - review & editing. **Ellen-Margrethe Hauge:** Investigation, Methodology, Supervision, Validation, Writing - review & editing. **Dennis McGonagle:** Investigation, Methodology, Supervision, Validation, Writing - review & editing. **Tue Wenzel Kragstrup:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing - review & editing.

Declaration of Competing Interest

TWK has engaged in educational activities receiving speaking fees from Pfizer, Bristol-Myers Squibb, Eli Lilly, Novartis, and UCB and has received a consultancy fee from Bristol-Myers Squibb and Gilead. TWK is co-founder and clinical developer in iBiotech ApS developing diagnostic and therapeutic solutions for people with autoimmune diseases and cancer. TWK has received the Gilead Nordic Fellowship grant.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2021.102829.

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