REVIEW ARTICLE

Hypertension: a new treatment for an old disease? Targeting the immune system

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Arterial hypertension represents a serious public health problem, being a major cause of morbidity and mortality worldwide. The availability of many antihypertensive therapeutic strategies still fails to adequately treat around 20% of hypertensive patients, who are considered resistant to conventional treatment. In the pathogenesis of hypertension, immune system mechanisms are activated and both the innate and adaptive immune responses play a crucial role. However, what, when and how the immune system is triggered during hypertension development is still largely undefined. In this context, this review highlights scientific advances in the manipulation of the immune system in order to attenuate hypertension and end-organ damage. Here, we discuss the potential use of immunosuppressants and immunomodulators as pharmacological tools to control the activation of the immune system, by non-specific and specific mechanisms, to treat hypertension and improve end-organ damage. Nevertheless, more clinical trials should be performed with these drugs to establish their therapeutic efficacy, safety and risk–benefit ratio in hypertensive conditions.

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Abbreviations

2K1C, two kidneys, one clip; AngII, angiotensin II; APC, antigen-presenting cell; C, complement; CD40L, ligand of CD40; CsA, cyclosporine; CTLA4, cytotoxic T-lymphocyte-associated protein 4; DAMPs, damage-associated molecular patterns; DOCA, deoxycorticosterone acetate; DSS, Dahl salt-sensitive; KO, knockout; mAb, monoclonal antibody; MAC, membrane attack complex; MR, mineralocorticoid receptor; mTOR, mammalian target of rapamycin; nAb, neutralizing antibody; NLR, nucleotide-binding oligomerization domain-like receptor; NLRP, nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing protein; NOD, nucleotide-binding oligomerization domain; OKT3, muromonab-CD3; PAMPs, pathogen-associated molecular patterns; PDTC, pyrrolidine dithiocarbamate; PRR, pattern recognition receptor; SHR, spontaneously hypertensive rats; SLE, systemic lupus erythematosus; TCR, T-cell receptor; TLRs, toll-like receptors; Treg, T regulatory cell; WT, wild-type

Introduction

For many years, cardiovascular diseases have been the major cause of death and disability worldwide. Raised levels of BP amplify the risk of cerebrovascular and coronary heart disease, making BP control the primary goal in the treatment of any cardiovascular disease. Based on the predictive value of BP level thresholds for adverse cardiac outcomes, some American guidelines have assumed more aggressive values for the definition of hypertension, which now are above 130–139 for systolic or 80–89 mmHg for diastolic pressures (Whelton *et al*., 2018).

Interventions that effectively lower BP directly affect hypertension-associated morbidity and mortality. In pharmacological terms, several classes of drug are clinically available, based on the classical view of BP control by the nervous system, vascular and renal mechanisms. Sympatholytic agents, natural alkaloids (**reserpine**) and semi-synthetic agents (**methyldopa**) were the earlier antihypertensive drugs, forerunners of the modern treatments (Sever and Messerli, 2011). Progressively, they were replaced by safer agents in an attempt to avoid their central depressor effects. From the 1950s to 2010, vasodilators, such as **hydralazine**, calcium channel blockers and renin–angiotensin system (RAS) blockers, emerged from the progress in our understanding of the mechanisms of vascular tone control, aiming to decrease peripheral vascular resistance (Sever and Messerli, 2011). Almost in parallel, thiazides and thiazide-like diuretics were introduced into the management of hypertension (Moser and Feig, 2009), whose antihypertensive effect results from the diuretic-induced reduction in systolic volume and an non-specific reduction in vascular resistance.

Certainly, the modern therapy of hypertension has reduced fatal and non-fatal outcomes and decreased end-organ damage (Ettehad *et al*., 2016). However, the current treatments have some limitations. For instance, ethnicity (Brewster *et al*., 2016), genetic variability (Chan *et al*., 2012b; Shahin and Johnson, 2016; Heidari *et al*., 2017; Ware *et al*., 2017) and phenotypic differences still determine tolerability and efficacy of antihypertensive drugs. Moreover, about 5 to 20% of hypertensive patients do not achieve BP control, even with combined agents from different pharmacological classes, and are categorized in a resistant or refractory phenotype of the disease (Siddiqui and Calhoun, 2017). Both terms refer to a failure to reduce BP, the former with three or more and the latter with five or more medications. At present, the clinical pharmacological principle of combination therapy is to target different mechanisms of BP control (nervous system, vascular and renal), and the existence of resistant and refractory patients illustrates the need for additional therapies.

With this background, studies on the immune basis of hypertension in animal models have discovered several targets and have encouraged studies in human populations using immunosuppressant agents. However, limited progress has been made in the clinical settings. Even traditional antihypertensive therapies have immunomodulatory effects that play a role in hypertension. This review highlights scientific advances made in the manipulation of the immune system, as a target in the attenuation of hypertension, vascular inflammation and end-organ damage. Here, we discuss the potential use of immunosuppressants and immunomodulators as pharmacological tools to control the activation of the immune system, by non-specific and specific mechanisms, to treat hypertension and improve end-organ damage. We also provide a risk/benefit evaluation for these drugs (Figure 2), based on the preclinical and clinical evidence.

An overview of immune responses in hypertension

The main function of the immune system is defending a host against antigens. For this purpose, the organism relies on a complex interplay between the two main arms of the immune system: the innate immunity, which mediates the early reactions, and the adaptive immunity, which is a late and more specific response (Figure 1). Damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) are the antigens that initially activate the immune system. In hypertension, DAMPs are known to be increased and are responsible for the chronic inflammation present in this condition. The origins of DAMPs are uncertain and much discussed. **Angiotensin II** (AngII), HMGB-1, **HSP60** and HSP70, **fibrinogen**, **uric acid** and mitochondrial DNA (see McCarthy *et al*., 2014) are the main molecules recognized as DAMPs in hypertension, whose levels are chronically elevated. DAMPs and PAMPs are recognized by **pattern recognition receptors (PRRs)** and start the immune response activation, as described below.

Innate immune response

The immune system has different cell types to perform its function. Macrophages, dendritic cells (DCs) and neutrophils are the main cell types involved in the innate immune response. DCs are seen as a source of DAMPs in hypertension, as there is an enhancement in **NADPH oxidase**-dependent superoxide production in DCs, which leads to the formation of highly reactive γ-ketoaldehydes, also known as isoketals or isolevuglandins (Kirabo *et al*., 2014). These compounds rapidly form self-proteins adducts, which are processed and presented as DAMPs by DCs, promoting renal and vascular dysfunction and hypertension.

Macrophage infiltration into vascular wall, the kidneys and myocardium (Justin Rucker and Crowley, 2017; Hulsmans *et al*., 2018) has been described in experimental models and patients with hypertension. Also, genetic deficiency of macrophages protected mice from vascular dysfunction and attenuated BP increase induced by AngII (De Ciuceis *et al*., 2005) and deoxycorticosterone acetate (DOCA)-salt hypertension (Ko *et al*., 2007). Macrophages are classified as 'M1' and 'M2' according to the effects that these two populations have on the differentiation of T-lymphocytes. Specifically, M1 macrophages are known to activate and guide Th1 lymphocytes, and M2 macrophages are associated with the induction of Th2 lymphocyte responses. Despite some data showing the contribution of macrophages in hypertension, there is a paucity of information about the polarization of M1 and M2 phenotype in this disease. Nevertheless, based on the T-lymphocyte interaction with macrophage subsets, there is indirect evidence of the role of macrophage polarization in hypertension.
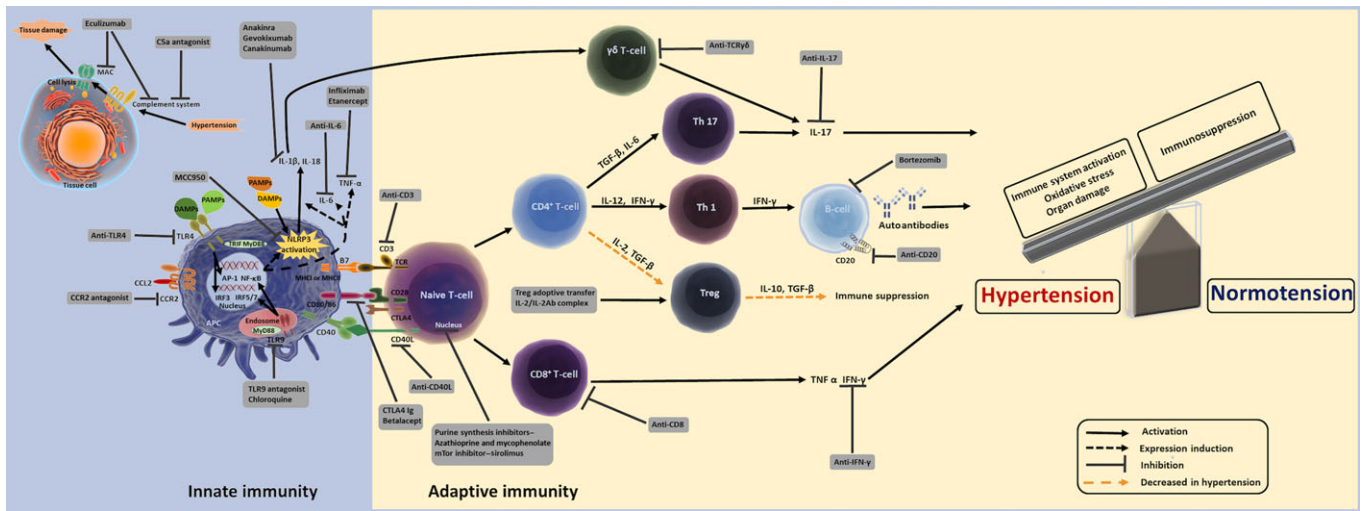
Figure 1

Targets in the immune system for the treatment of hypertension. The unregulated and persistent activation of the immune system, cytokine release and oxidative stress induce cardiovascular organ damage and, consequently, hypertension. Drugs available to modulate the immune response and likely to control BP and improve end-organ damage are shown in the grey boxes. The dashed orange arrows indicate a diminished response, while black arrows indicate activated mechanisms. More details about the drugs are found in the main text. Based on patient risk/benefit ratio profile of targeted therapies, immune system modulation may provide a new strategy to treat hypertension. AP-1, activator protein 1; IRF3, IFN regulatory factor 3; MyD88, myeloid differentiation response 88 protein; Tac, tacrolimus; TRIF, toll/IL-1 receptor homologous region domain-containing adapter-inducing IFN-β.

NK cells are a cytotoxic cell type with non-specific functions and, for this reason, it is considered to be part of the innate response. NK cells produce a variety of inflammatory cytokines and growth factors, such as **IFN-γ**, **TNF-α** and GM-CSF. Depletion of NK cells, using an anti-NK antibody, protects against AngII-induced vascular dysfunction (Kossmann *et al.*, 2013).

The complement system is an essential component of humoral and natural immunity. Complement activation occurs through classical, alternative and lectin pathways. These events converge in the activation of the **complement (C)3** convertase and formation of **C5** convertase, which cleaves C5 into the **C5a**, C5b and other fragments. The complement fragments act as potent pro-inflammatory anaphylatoxins stimulating immune cell recruitment and activation and, especially, leading to membrane attack complex (MAC) formation. The formation of MAC results in cell lysis and also triggers inflammation (Horiuchi and Tsukamoto, 2016). In hypertensive mice, complement activation was associated with renal damage (Raij *et al.*, 1989; Shagdarsuren *et al.*, 2005) but was not involved in aortic and cardiac remodelling (Coles *et al.*, 2007). Also, MAC deposition in renal biopsies from systemic lupus erythematosus (SLE) patients correlates with higher systolic BP (Wang *et al.*, 2018b). Therefore, complement inhibition can contribute to control of organ damage in hypertension.

Pattern recognition receptors

The involvement of PRR in hypertension has been extensively investigated and has become determinant (Bomfim *et al.*, 2017). Initially, PAMPs or DAMPs are recognized by immune cells by the PRR, expressed in cellular membranes or inside the cells. The main families of PRR that have been described are **toll-like receptors (TLRs)**, **retinoic acid-inducible gene I-like helicases** and nucleotide-binding oligomerization domain **(NOD)-like receptor (NLR)**. Despite the fact that other PRRs have been reported, only two types have been investigated in hypertension: TLR and NLR. These receptors recognize PAMPs and DAMPs and initiate the immune response of the host (Liew *et al.*, 2005; Takeda and Akira, 2005). Their activation leads to the production of pro-inflammatory cytokines, chemokines, tissue-destructive enzymes and type I IFNs by host cells. In the case of NLR, some subtypes as NLR family pyrin domain-containing protein **(NLRP)1** and **NLRP3** induce inflammasome activation, which leads to **IL-1β** and **IL-18** maturation.

Several TLR subtypes seem to be involved in hypertension such as **TLR2**, **TLR3**, **TLR4**, **TLR7/TLR8** and **TLR9**. TLR4 was up-regulated in the cardiovascular system of different hypertensive models, such as in spontaneously hypertensive rats (SHR) (Bomfim *et al.*, 2012), and hypertension induced by **L-NAME** (Eissler *et al.*, 2011). Regardless of the hypertensive model used, they all display hypertension-associated end-organ damage (Eissler *et al.*, 2011). In general, TLR4 plays a role in vascular dysfunction, cardiac and renal injury and dysregulation of the CNS in hypertension (Biancardi *et al.*, 2017). Treatment with anti-TLR4 showed good results decreasing BP in different models of hypertension (Bomfim *et al.*, 2012; Hernanz *et al.*, 2015) (Table 1). Indeed, L-NAME-induced hypertension was blunted in TLR4 knockout (KO) when compared with wild-type (WT) mice (Sollinger *et al.*, 2014). However, TLR4-deficient mice infused with AngII presented marked inhibition of vascular remodelling, although there was no change in BP levels when compared with WT mice infused with AngII (Nakashima *et al.*, 2015). Also, high-salt-diet-induced pre-hypertension was associated with increased TLR4 and pro-inflammatory cytokines in the

Table 1

Drugs aimed at the innate and adaptive immune systems as pharmacological targets in hypertension

Immune target	Drug	Experimental model	Experimental outcome	Clinical perspective or limitation
Classical agents				
All immune cells (alkylating agent)	Cyclophosphamide	SHR and DOCA-salt (Khraibi et al., 1984)	↓ BP in SHR but not in DOCA-salt rats.	Intense cardiotoxic effects (Curigliano et al., 2016).
Thymocyte	Anti-thymocyte serum	SHR (Bendich et al., 1981)	↓ BP.	Serum sickness-like reactions are common adverse effects, and cytokine release syndrome appears to be involved (Chen et al., 2015).
mTORC1	Rapamycin (sirolimus)	DSS rats (Kumar et al., 2017)	↓ BP, ↓ kidney injury and hypertrophy and ↓ kidney T-lymphocytes (CD3⁺) and macrophage (ED1⁻) infiltration.	Associated with high incidence of hypertension (Olyaei et al., 2005).
Purine metabolism	Azathioprine	DOCA-salt pregnant rats (Tinsley et al., 2009)	↓ BP, ↓ proteinuria, ↓ IL-2, ↓ IL-12, ↓ IFN-γ, ↓ chemokines and ↓ endothelial dysfunction.	Associated with high incidence of hypertension (Olyaei et al., 2005).
IMPDH	Mycophenolate	SHR (Rodriguez-Iturbe et al., 2002), DOCA-salt pregnant rats (Tinsley et al., 2009), DOCA-salt rats (Boesen et al., 2010) and SLE mice (Taylor and Ryan, 2017)	↓ BP, ↓ proteinuria, ↓ IL-2, ↓ IL-12, ↓ IFN-γ, ↓ chemokines, ↓ endothelial dysfunction, ↓ renal cortical T-lymphocyte and macrophage infiltration, ↓ albuminuria and creatinine clearance, selectively depleted CD45R⁺ B-cells and ↓ subsequent autoantibody production.	↓ hypertension in patients with autoimmune diseases, probably through the reduction of TNF-α, chemokines and oxidative stress (Herrera et al., 2006).
Innate immune response				
TLR signalling				
TLR4	Anti-TLR4	SHR (Bomfim et al., 2012)	↓ BP, ↓ TLR4 expression, ↓ serum IL-6, ↓ endothelial dysfunction, ↓ Cox-2 expression and ↓ TxA2 release.	Phase I studies demonstrated a safe profile of anti-TLR4 (Monnet et al., 2017).
		SHR (Echem et al., 2015)	BP not altered, ↓ TLR4 expression, ↓ MyD88 expression, ↓ NF-κB activation, ↓ IL-1β and TNF-α cardiac expression, ↓ cardiac hypertrophy, ↓ cardiac fibrosis and ↓ cardiac remodelling.	
		AngII-infused mice (Hernanz et al., 2015)	↓ BP, ↓ endothelial dysfunction, ↓ vascular remodelling, ↓ collagen	

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Table 1
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Immune target	Drug	Experimental model	Experimental outcome	Clinical perspective or limitation
			deposition, ↓NOX-1 mRNA levels, ↓JNK1/2, ↓NF-κB activation, ↓IL-1β, ↓TNF-α, ↓CCL2, ↓NADPH oxidase activity, ↓oxidative stress and ↑NO release.	
TLR9	Chloroquine	SHR (McCarthy et al., 2017)	↓BP, ↓MyD88 and TRAF6, ↓NF-κB activation, ↓LVH, ↓aortic immune cell recruitment and infiltration, ↓aortic total leukocytes (CD45+), ↓serum T-cells (CD3+) and ↓CD44+ on T-cells (CD3+).	Long therapeutic regimes with chloroquine occasionally lead to cardiac conduction disorders and cardiomyopathy (Al-Bari, 2015).
NF-κB	PDTC	SHR (Rodriguez-Iturbe et al., 2005)	↓BP, ↓NF-κB activation, ↓ICAM-1, ↓MCP-1, ↓lymphocyte and macrophage renal infiltration and ↓renal malondialdehyde.	No tolerability test was performed in humans.
		2K1C rats (Cau et al., 2015; Cau et al., 2011)	↓BP, ↓endothelial dysfunction, ↓aortic and cardiac remodelling, ↓oxidative stress and ↓MMP-2 and MMP-9 levels and activity.	
TNF-α	Infliximab	SHR (Filho et al., 2013)	↓BP and ↓LVH, ↑AKT/eNOS phosphorylation and ↓JNK and NF-κB activation.	Infliximab infusion may result in cytokine release syndrome, anaphylactic reactions and fever with degranulation of mast cells and basophils (Lichtenstein et al., 2015). TNF-α blockade was associated with higher risk of infection diseases, heart failure and elevation of PVR, SBP and DBP (Sinagra et al., 2013; Zhao et al., 2015).
TNFR2	Etanercept	Fructose-fed hypertensive rats (Tran et al., 2009),	↓BP, ↑vascular function and restored eNOS expression.	
		SLE mice (Venegas-Pont et al., 2010)	↓BP, ↓NF-κB activation, ↓BP, ↓macrophage renal infiltration and ↓albuminuria.	
TNFR2/IL-1R	TFI	AngII-infused mice (Wang et al., 2014)	No changes in BP, ↓cardiac damage and ↓leukocyte adhesion and migration responses.	
IL-6	IL-6 nAb	DSS rats (Hashmat et al., 2016)	↓BP, ↓renal monocyte and macrophage (CD11b/c+) infiltration and ↓glomerular injury index.	Tocilizumab treatment did not increase cardiovascular risk or events (Kim et al., 2017).

Table 1

(Continued)

Immune target	Drug	Experimental model	Experimental outcome	Clinical perspective or limitation
NLR signalling				
NLRP3	MCC950	DOCA-salt mice (Krishnan et al., 2016)	↓ BP, ↓ renal IL-6, ↓ IL-17A, ↓ TNF and ↓ osteopontin.	Canakinumab has just been approved for clinical use and has proved to lower chances of recurrent cardiovascular events (Shah et al., 2018).
IL-1β	Gevokizumab	I.c.v. injection in DSS rats (Qi et al., 2016)	↓ BP, ↓ HR, ↓ plasma noradrenaline, ↓ oxidative stress and restored cytokine balance.	
	Anakinra	DOCA-salt in mice (Ling et al., 2017)	↓ BP, ↓ renal CCL2, CCL5, ↓ renal collagen deposition but ↑ renal hypertrophy.	
		Ang II-infused mice (Zhang et al., 2016)	↓ BP and ↓ cardiac hypertrophy.	
Adaptive immune response				
T-cell and APC interaction				
CTLA4	CTLA4-Ig	AngII-infused and DOCA-salt mice	↓ BP, ↓ T-cell activation, ↓ cytokine release and ↓ vascular inflammation.	Risk of infections, gastrointestinal disorders and headache; belatacept was associated with no changes in BP but ↓ aortic augmentation pressure (Seibert et al., 2014).
CD40L	Anti-CD40L (Cornelius et al., 2015)	Pre-eclampsia in rats	↓ BP, ↓ placental oxidative stress and ↓ AT1R.	Incidence of thrombotic events (Sidiropoulos and Boumpas, 2004).
Ubiquitin–proteasome system				
Proteasome	Bortezomib	AngII-infused mice (Li et al., 2013) and SLE mice (Taylor et al., 2018a)	↓ BP, ↓ vascular remodelling, ↓ ROS generation and ↓ VCAM-1.	Haematological, gastrointestinal and neurological toxicities (Bross et al., 2004).
T-cells and B-cells				
CD3	Muromonab	SLE in female mice (Mathis et al., 2017)	↓ BP and spleen weight, ↓ expression of IL-17RA, but it did not reduce renal injury nor TNF-α expression.	Risk of cytokine release syndrome, which can result in multiple organ damage (Bugelski and Martin, 2012).
Treg	IL-2/IL-2Ab complex	AngII-infused mice (Majeed et al., 2014)	No effect in BP but ↓ vascular stiffness, ↑ Treg in spleen, ↓ Th17 and macrophages in aorta.	No human tests so far.
		Transverse aortic constriction (Wang et al., 2016)	No effect in BP but ↓ congestive heart failure.	
	Treg adoptive transfer	AngII-infused mice (Barhoumi et al., 2011;	↓ BP, ↓ cardiac hypertrophy, inflammation and fibrosis,	Clinical limitation due to the difficulty in acquiring Treg cells for treatment.

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Table 1
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Immune target	Drug	Experimental model	Experimental outcome	Clinical perspective or limitation
CD8	Anti-CD8	Kvakan et al., 2009; Matrougui et al., 2011)	↓ vascular injury and improved coronary arteriolar dysfunction.	Weak evidence for its use in hypertension, and no clinical tests were performed yet.
CD20	Anti-CD20	AngII-infused mice (Ma et al., 2014)	No effect in BP but ↓ cardiac profibrogenic inflammation.	Immunosuppression, infections, renal toxicity and cardiac arrhythmias (Hansel et al., 2010).
TCRγδ	anti-TCRγδ	AngII-infused mice (Chan et al., 2015)	↓ BP and ↓ vessel remodelling.	In vitro assays showed that anti-TCRγδ stimulate human γδ T-cells from peripheral blood, which brings the question if anti-TCRγδ would be safe in hypertension (Zhou et al., 2012).
		AngII-infused mice (Caillon et al., 2017)	↓ BP, γδ T-cell depletion and ↓ endothelial dysfunction.	
IL-17	IL-17A mAb	AngII-infused mice (Saleh et al., 2016)	↓ BP, ↓ albuminuria, ↓ renal and aortic infiltration of total leukocytes, ↓ total T-cells (CD3⁺), ↓ T helper (CD4⁺), ↓ T-cytotoxic (CD8⁺), ↓ renal TGF-β, blunted TH17, ↓ ROS, ↓ autoantibodies, ↑ Tregs in spleen and lymph node and ↓ aortic endothelial dysfunction.	In normotensive patients, brodalumab (IL-17RA mAb) demonstrated cardiovascular safety (Papp et al., 2016).
	IL-17 nAb	Calcineurin inhibitor-induced hypertension (Chiasson et al., 2017)		
	IL-17RC	Pre-eclampsia in rats (Cornelius et al., 2013)		
IL-17AR	IL-17AR mAb	AngII-infused mice (Saleh et al., 2016)	↓ BP, ↓ albuminuria, ↓ renal and aortic infiltration of total leukocytes, ↓ total T-cells (CD3⁺), ↓ T helper (CD4⁺), ↓ T-cytotoxic (CD8⁺), ↓ renal TGF-β and ↓ organ damage.	
IFN	IFN-γ nAb (Sun et al., 2017)	Mice overexpressing MR after AngII infusion	↓ BP.	Increase the patient's risk of infection (Kelchtermans et al., 2008).

AT1R, angiotensin II AT$_1$ receptor; DBP, diastolic BP; ED1⁺, macrophage marker; eNOS, endothelial NOS; HR, heart rate; ICAM-1, intercellular adhesion molecule 1; IL-17RC, IL-17 recombinant receptor C; IMPDH, inosine monophosphate dehydrogenase; LVH, left ventricular hypertrophy; mTORC1, mammalian target of rapamycin complex 1; MyD88, myeloid differentiation response 88 protein; NOX-1, catalytic subunit of NADPH oxidase (also known as gp91phox); PVR, peripheral vascular resistance; SBP, systolic BP; TFI, TNF receptor 2 fragment crystallization IL-1 receptor antagonist; TNFR2, TNF receptor 2; TRAF6, TNF receptor-associated factor 6; VCAM-1, vascular adhesion molecule 1.

paraventricular nucleus (PVN) of rats. More importantly, PVN infusion of a TLR4 antagonist reduced BP, pro-inflammatory cytokine expression and oxidative stress (Wang *et al.*, 2018a).

Besides TLR4, other subtypes also contribute to hypertension. Expression of TLR2 was augmented in the kidney of rats infused with AngII (Ahn *et al.*, 2007) and TLR9 activation was associated with vascular dysfunction in SHR (McCarthy *et al.*, 2015). TLR3 and TLR7/TLR8 have not been directly investigated in a hypertensive model, but are important in pre-eclampsia, which is a pregnancy-specific hypertensive syndrome characterized by excessive maternal immune system activation, inflammation and endothelial dysfunction. Genetic expression levels of TLR3, TLR7 and TLR8 were significantly increased in women with pre-eclampsia compared with normotensive pregnant women (Chatterjee *et al.*, 2012). Treatment of human trophoblasts with a TLR3 (**polyinosine–polycytidylic acid**), TLR7 [**imiquimod** (R-837)] or TLR7/TLR8 (CL097) agonists enhanced the expression levels of TLR3/TLR7/TLR8 and caused pregnancy-dependent hypertension (Chatterjee *et al.*, 2012). TLR9 activation (CpG ODN) during gestation caused maternal hypertension and increased contractile responses in resistance arteries (Goulopoulou *et al.*, 2016).

NLRP3 is the most studied NLR in the context of cardiovascular diseases. NLRP3 gene polymorphisms were associated with higher systolic and diastolic BP in 50-year-old patients (Kunnas *et al.*, 2015). The two kidneys, one clip (2K1C) and DOCA-salt hypertensive mouse models exhibited enhanced renal expression of NLRP3 and IL-1β. Accordingly, NLRP3 KO mice did not develop hypertension when submitted to 2K1C hypertension and DOCA-salt treatment (Wang *et al.*, 2012).

Other NLR subtypes have also been investigated in hypertension. Stimulation of **NOD1** in mice promoted haemodynamic changes such as decreased BP, increased heart rate and vascular hyporesponsivity to contractile agonists (Cartwright *et al.*, 2007). In humans, the **NOD2** gene locus has been associated with hypertension (Gu *et al.*, 2007) and the NLRP6 angiotensin–vasopressin receptor loci may contribute to susceptibility to essential hypertension, because vasopressin binds to NLRP6 with high affinity (Glorioso *et al.*, 2013).

Adaptive immune responses

The contribution of adaptive immune responses, represented by lymphocytes and antibodies, to hypertension has been extensively investigated in the last decade. Hypertension in humans and SHR is associated with enhanced serum levels of IgG, IgA or IgM antibodies (Hilme *et al.*, 1989; Chen and Schachter, 1993).

Many researchers have used animal models with depletion of adaptive immune cells and cytokines to show the association of lymphocytes with hypertension. For example, mice with inactivation of the recombination-activating gene 1 (Guzik *et al.*, 2007), which lack T-lymphocytes and B-lymphocytes; severe combined immunodeficiency mice lacking lymphocyte responses (Crowley *et al.*, 2010); **IL-17** KO mice (Kamat *et al.*, 2015); mice with adoptive transfer of T regulatory cell (Treg) (Barhoumi *et al.*, 2011); and mice genetically deficient in B-cells, **B-cell-activating factor receptor** KO (Chan *et al.*, 2015), all exhibit attenuated hypertension in response to AngII.

B-cells play an essential role in adaptive immunity to detect and process antigens with further differentiation in plasma cells with antibody production. AngII infusion was associated with increased splenic B-cells expressing **CD86**, splenic plasma cell, circulating IgG and marked IgG accumulation in the aortic adventitia (Chan *et al.*, 2015).

Regarding **CD4** T-cell participation in hypertension, studies demonstrated a Th1 and Th17 lymphocyte polarizing response, which may be characterized by IFN-γ and IL-17 release from Th1 and Th17 respectively. Also, hypertension decreased responses of Th2 and Treg lymphocytes.

IFN-γ KO mice were protected from AngII-induced vascular and kidney dysfunction (Kossmann *et al.*, 2013; Kamat *et al.*, 2015). Th1 cells are important IFN-γ producers. Th17 and γδ T-cells are the primary sources of IL-17A in AngII-induced hypertension (Saleh *et al.*, 2016) and play an essential role in the pathogenesis of hypertension in specific cases. IL-17 KO mice demonstrated preserved endothelial function and attenuation of hypertension after exposure to AngII (Madhur *et al.*, 2010). DOCA-salt rats exhibited elevated levels of RAR-**related orphan receptor γ T**, the transcription factor for Th17 and increased IL-17 expression in spleen, the heart and the kidney (Amador *et al.*, 2014). Accordingly, hypertension induced by AngII was not sustained in IL-17 KO mice, which displayed preserved vascular function, decreased superoxide production and reduced aortic T-cell infiltration (Kamat *et al.*, 2015). Although Th17 cells are a source of IL-17, Chen *et al.* (2014) suggested that γδ T-cells are the most important source of IL-17 in hypertension, representing a crucial cell type during the development of hypertension.

Regulatory T-lymphocytes (Treg) are cells that suppress the immune response and maintain self-tolerance. Many mechanisms have been proposed for the suppressor function of these cells. These mechanisms include the secretion of suppressive cytokines (**IL-10**, **TGF-β** and IL-35), direct cytolysis of effector T-cell, metabolic disruption through **tryptophan** catabolites, **IL-2** deprivation and direct interference of co-stimulation *via* expression of cytotoxic T-lymphocyte-associated protein 4 (**CTLA-4**) (Davidson and Shevach, 2011). Treg cells have a protective effect in hypertension, mainly in AngII-induced hypertension and AngII induced Treg apoptosis (Matrougui *et al.*, 2011). Also, adoptive transfer of Treg prevented AngII-induced hypertension, vascular damage and vascular immune cell infiltration (Barhoumi *et al.*, 2011). Kvakan *et al.* (2009) also described decreased cardiac hypertrophy and less cardiac fibrosis with an improvement in arrhythmogenic electric remodelling after adoptive transfer of Treg cells into AngII-infused hypertensive mice.

CD8 T-cells have an important specific cytotoxic function. CD8 T-cells also play a role in hypertension. Recently, Youn *et al.* (2013) demonstrated that pro-inflammatory immunosenescent CD8 T-cells were enhanced in humans with hypertension, suggesting a clonal expansion of a unique population of CD8 T-cells in hypertension. Another study demonstrated that AngII infusion in WT and CD4 KO mice resulted in increased systolic and diastolic BP. However, BP elevation was blunted in CD8 KO mice under AngII infusion. They also induced DOCA-salt hypertension in WT, CD8 KO and CD4 KO mice and had similar results of AngII infusion in mice. Also, adoptive transfer of $CD4^+/CD25^-$ cells from

AngII-treated mice to RAG-1 KO mice had no effect on BP, but the adoptive transfer of CD8^{+} cells caused BP elevation (Trott *et al*., 2014).

Antihypertensive treatments and immune system

Several antihypertensive treatments have been proposed over the years, such as lifestyle modifications, pharmacological therapies and even surgical intervention. To date, the association between the activation of the immune system and hypertension has become clearer. Nevertheless, it is still unclear whether immune activation is a cause or a consequence, of increased BP. In fact, there is indirect evidence that high BP *per se* may affect the immune system. For example, many antihypertensive treatments may act as modulators of the immune system alongside BP reduction, which may be responsible for some of their beneficial effects. However, to our knowledge, no study has systematically addressed the effects of BP *per se* on the immune system, and studies addressing this issue are warranted. Therefore, evidence showing modulation of the immune system by antihypertensive treatment will be discussed.

Salt restriction

An important non-pharmacological strategy to control BP is the reduction of salt consumption. Besides its effects on systolic volume enhancement and, consequently, BP increase, high-sodium diet is intimately linked to the polarization of Th naïve cells to Th17 and elevated IL-17A production (Kleinewietfeld *et al*., 2013). In salt-dependent and salt-independent models of hypertension, the deletion of a salt-sensing enzyme in T-lymphocytes impairs the development of hypertension, Th17 polarization and end-organ damage (Norlander *et al*., 2017). In this sense, salt restriction could represent an intervention to control immune response in hypertension. However, salt-restricted diets in hypertensive patients led to mild BP attenuation with markers of immune system activation, such as enhanced C-reactive protein concentration and elevated TNF-α and **IL-6** levels (Nakandakare *et al*., 2008). These findings suggest that the BP control by salt restriction is, at least in part, dependent on the down-regulation of the immune system. Thus, it is possible that hypertensive patients can achieve more efficient BP control with pharmacological therapies focusing on the down-regulation of the immune system in parallel with salt restriction.

Calcium channel blockers

Calcium channel blockers (CCBs), which control BP mainly through reduction of calcium influx in the peripheral vascular bed, were already known to negatively modulate the immune system in different *in vitro* (Rodler *et al*., 1995) and *in vivo* (Katoh *et al*., 1997) studies. After that, studies focusing on CCB immunomodulation on the treatment of hypertension appeared. **Nifedipine** reduced the mRNA for CCL2 by **NF-κB** inhibition-dependent mechanisms in rat vascular smooth muscle cells exposed to AngII (Wu *et al*., 2006). In addition, **amlodipine** prevented the expression of aortic NADPH oxidase, **vascular cell adhesion molecule 1** and

CCL2 in L-NAME-induced hypertensive rats in a pressure-independent manner (Toba *et al*., 2005). Recently, hypertensive left ventricular hypertrophy was shown to be partly dependent on the activation of a member of the TNF superfamily and that amlodipine could reverse this effect in SHR. (Lu *et al*., 2016). It is likely that the effects of amlodipine and other CCBs on the cardiovascular system are due, not only to their vasodilator properties, but also through down-regulation of specific components of innate and adaptive immunity. However, more experimental and clinical studies on the effects of CCBs on hypertension are encouraged, in order to elucidate the connections between the long-term benefits of CCBs and regulation of the immune system.

Renin–angiotensin aldosterone system (RAS) blockade

Blockade of the RAS with **angiotensin-converting enzyme** inhibitors (ACEi) or **AT$_1$** receptor antagonists is the first-choice treatment for hypertension in the present day. These drugs also modulate the immune system, which could contribute to antihypertensive effects and organ damage protection. Under physiological conditions, for example, ACE inhibition by **enalapril** enhanced splenic CD4^{+}CD103^{+}CD25^{−} Treg production and response in Balb/c mice (Albuquerque *et al*., 2010). In lupus nephritis-associated hypertension, the attenuation of BP by ACEi involves the reduction of Th2 polarization, cytokine production and renal damage (De Albuquerque *et al*., 2004). Also, ACE interferes with both major histocompatibility complex (MHC)I and MHCII antigen-presenting processes and increases innate and adaptive immune responses (Bernstein *et al*., 2018). Therefore, it is expected that ACEi would promote a negative modulation on presenting processes of hypertensive patients and, consequently, reduce BP and organ damage. A similar effect was observed by Hevia *et al*. (2018), as the ablation of antigen-presenting cells prevented hypertension, cardiac hypertrophy and renal inflammation in mice submitted to AngII plus high-salt diet. However, this hypothesis remains untested, and the relationship between immune response and other modes of RAS blockade also needs further study.

In SHR-stroke resistant (SHR-SR), the AT$_1$ receptor antagonist, **telmisartan**, was tested at low and high doses, and NLRP3 activation was assessed. Telmisartan attenuated hypertension only at high doses while it inhibited NLRP3 inflammasome from the neurovascular unit in a dose-dependent manner (Liu *et al*., 2015). These findings suggest that telmisartan inhibition of NLRP3 is BP-independent, and for this reason, it could be related to vascular function improvement. In hypertensive patients, **losartan** decreased T-cell activity (Sonmez *et al*., 2001), and in combination with **atorvastatin** and **captopril**, it down-regulated serum levels of IL-6 (Sepehri *et al*., 2016).

Aldosterone, through action at the **mineralocorticoid receptor (MR)**, is the main mediator of volume retention after RAS activation. **Spironolactone**, an MR antagonist, demonstrated a different immunomodulatory pattern from other RAS blockers. In DOCA-salt hypertension, spironolactone treatment reduced Th17 response and IL-17 production and enhanced Treg response (Amador *et al*.,

2014). This mechanism appears to be related to spironolactone-prevented hypertension, as anti-IL-17 treatment effectively attenuated hypertension, as did spironolactone (Amador *et al.*, 2014). Spironolactone also demonstrated potent inhibition of leukocyte migration (Hofbauer *et al.*, 2002), which may have contributed to its down-regulation of the immune system. However, the exact mechanism(s) involved in this down-regulation of the immune system by MR antagonists is not entirely understood. Although there is only limited knowledge from clinical studies on immunomodulation by MR antagonists, in hypertensive patients, spironolactone efficiently controlled BP, preserved endothelial function and reduced inflammation, as shown by reduced C-reactive protein (Yamanari *et al.*, 2009).

Diuretics

Besides MR antagonists, thiazide and loop diuretics are also prescribed for BP control, with or without other antihypertensive drugs. Although the effect of diuretics on the immunomodulation in hypertension is controversial, it is possible to find relevant evidence on diuretics as hypertensive treatments and their effects on the immune system.

For instance, thiazide diuretics up-regulated the immune system of recently diagnosed hypertensive patients, enhancing IgM anti-ApoB-D autoantibodies (Fonseca *et al.*, 2015). On the other hand, Toledo *et al.* (2015) observed that diuretic treatment down-regulated circulating levels of pro-inflammatory cytokines IL-6 and TNF-α in elderly hypertensive patients (Toledo *et al.*, 2015). Both studies claim that diuretic treatment improved BP and endothelial function in hypertensive patients, but they disagree concerning the immunomodulation triggered by diuretic drugs. It is possible that age differences may have influenced the findings and more studies are required to test the exact mechanism of immunomodulation by diuretics in hypertensive patients. In Dahl salt-sensitive (DSS) rats, for instance, **hydrochlorothiazide** and **chlorthalidone** were administered, and although BP was efficiently controlled, these diuretics did not attenuate oxidative stress and inflammation caused by hypertension (Zhou *et al.*, 2008). Combination of diuretics with other antihypertensive therapies has demonstrated to negatively immunomodulate and, consequently, improve hypertension diuretic treatment in both experimental (Jin *et al.*, 2014) and clinical studies (Agabiti-Rosei *et al.*, 2014). Therefore, long-term inflammation caused by diuretics should be considered as a potentially threatening condition, and additional pharmacological therapies to down-regulate the immune system in parallel to diuretic therapy may contribute to the treatment of hypertension.

Renal sympathetic denervation

Renal sympathetic denervation (RSD), a therapeutic strategy used in patients with resistant hypertension (Coppolino *et al.*, 2017), has also been reported as a modulator of the immune system (Xiao *et al.*, 2015; Zaldivia *et al.*, 2017). In addition to the attenuation of sympathetic activity and BP, bilateral RSD in AngII-exposed mice reduced albuminuria, dendritic cell activation, renal Th and T-cytotoxic infiltration, fibrosis, ROS, **IL-1α**, IL1-β and IL-6 (Xiao *et al.*, 2015). Similar effects on BP and inflammatory status were observed in clinical patients after 3 and 6 months of RSD procedure, in which the RSD significantly attenuated BP, plasma levels of CCL2, monocyte activation, **IL-12**, IL-1β and TNF-α (Zaldivia *et al.*, 2017). Also, a positive relationship was found between sympathetic activity and monocyte activation before and after RSD (Zaldivia *et al.*, 2017), which suggests that the therapeutic strategy of RSD partly includes the attenuation of monocyte activity and inflammation in hypertension. As a proof of concept, **nebivolol**, a selective antagonist of β1-adrenoceptors triggered similar immunomodulation. Nebivolol efficiently reduced innate immune responses in hypertensive patients after treatment, as shown by decreased levels of circulating neutrophils (Hussain *et al.*, 2017), oxidative stress and **intercellular adhesion molecule 1** (Serg *et al.*, 2012).

The down-regulation of the immune system appears as a key factor in the treatment of hypertension. Therefore, there is enough evidence that antihypertensive treatments may benefit hypertensive patients not only through its classical pathways but also through down-regulation of the immune system. Although different hypertensive therapies result in different pathways of immunomodulation, these pieces of evidence support the idea of immunosuppressant agents as potential therapeutic strategies for the treatment of hypertension. Furthermore, it suggests that immunosuppressant drugs may be beneficial to hypertensive patients in specific cases.

Immunosuppressants as antihypertensives

Classical agents

The contribution of immunological mechanisms to hypertension is now clearly demonstrated. Therefore, treatment with immunosuppressant drugs is the most intuitive attempt to translate basic science to the treatment of hypertensive patients. Immunosuppressant drugs t decrease the activity of the immune system and they were introduced in clinical practice mainly to prevent acute rejection of organ transplants, thus avoiding graft loss (Allison, 2000). They also comprise the treatment of autoimmune diseases, such as rheumatoid arthritis and SLE. From a classical view, these drugs can be grouped on the basis of their mechanisms of action (Allison, 2000): (i) regulators of gene expression (glucocorticoids), (ii) alkylating agents (**cyclophosphamide**), (iii) kinase and phosphatase inhibitors (**cyclosporine A**, **tacrolimus** and **rapamycin**) and (iv) inhibitors of nucleic acids synthesis (**azathioprine**, **mycophenolate mofetil** and **leflunomide**). Some of these drugs have also been tested in experimental models of hypertension, as summarized in Table 1.

The first pharmacological attempts to treat hypertension with immunosuppressants were performed in the 1980s when a polyclonal anti-thymocyte globulin and cyclophosphamide were given to SHR and hypertension was reversed (Bendich *et al.*, 1981; Khraibi *et al.*, 1984). Both studies with non-specific immunosuppressant drugs demonstrated that lymphocyte depletion was the primary mechanism involved in this mitigation of hypertension. Nowadays, these

therapies are considered unacceptable, due to the cytokine release syndrome, general toxicity and extensive exposure to infectious diseases.

The drugs in the third class of immunosuppressant include calcineurin inhibitors, cyclosporin A (CsA), tacrolimus and mammalian target of rapamycin (**mTOR**) inhibitors. CsA and tacrolimus are out of consideration as arterial hypertension and kidney dysfunction are well-recognized long-term side effect of these compounds (Hoskova *et al.*, 2017). These effects are not associated with the immunosuppression *per se* but with activation of the RAS and **endothelin** systems, increased sympathetic activity and diminished **NO** bioavailability (Hoorn *et al.*, 2012; Hoskova *et al.*, 2017). Also, a new calcineurin inhibitor, voclosporin, which was developed to achieve higher efficacy and lower toxicity, did not show any significant difference regarding the incidence of hypertension and adverse events after kidney transplantation compared with tacrolimus (Busque *et al.*, 2011).

mTOR inhibitors such as **everolimus**, **temsirolimus** and **sirolimus** appear as less cytotoxic pharmacological therapies to inhibit lymphocyte proliferation in a non-specific manner (see Figure 1) (Shimobayashi and Hall, 2014). Sirolimus attenuated hypertension and renal infiltration by T-lymphocytes and macrophages, in DSS rats (Kumar *et al.*, 2017) and decreased cardiac hypertrophy in SHR (Soesanto *et al.*, 2009) and heart transplant recipients (Kushwaha *et al.*, 2008). In contrast, the administration of sirolimus for 7 weeks induced hypertension in normotensive rats in consequence of its side effects such as dyslipidaemia, hyperglycaemia and proteinuria (Reis *et al.*, 2009). Therefore, sirolimus has clear limitations as an alternative treatment for hypertension (Figure 2).

The inhibitors of nucleic acid synthesis, such as azathioprine, leflunomide and mycophenolate mofetil, represent the last class of immunosuppressant, shown in Figures 1 and 2. Azathioprine, a purine analogue that inhibits *de novo* purine synthesis, attenuated proteinuria and hypertension, as well as reducing chemokines and pro-inflammatory cytokines in a model of pregnancy-induced hypertension in rats (Tinsley *et al.*, 2009). Similarly, mycophenolate mofetil, an **inosine monophosphate dehydrogenase** inhibitor, attenuated hypertension in DOCA-salt rats (Boesen *et al.*, 2010), SHR (Rodriguez-Iturbe *et al.*, 2002) and an SLE model (Taylor and Ryan, 2017). These effects were brought about by the improvement of renal function as a result of reduced renal infiltration of T-lymphocyte and macrophages (Tinsley *et al.*, 2009; Boesen *et al.*, 2010; Taylor and Ryan, 2017). Importantly, the treatment of patients with autoimmune diseases with mycophenolate mofetil was associated with BP reduction and reduced TNF-α and oxidative stress levels (Herrera *et al.*, 2006). Taken together, all these data demonstrate that, among the classical immunosuppressant drugs, mycophenolate mofetil has the most desirable risk/benefit balance (Figure 2).

As summarised above, the classical immunosuppressant drugs were disappointing in terms of their antihypertensive action. It is possible that more specific drugs, targeting particular molecules involved directly in the organization of immune responses, could overcome these limitations and be considered as treatments for hypertension.

# Immune targets for the treatment of hypertension involving the innate immune response

Monocyte/macrophage inhibition

Macrophages and neutrophils compose the most important effector cells of the innate immune response. The chemokine **CCL2** is a chemotactic factor for monocytes and a potential intervention point to treat hypertension. The absence of CCL2 reduced monocyte recruitment in the hearts of mice exposed to the hypertrophic stimulus and protected against diastolic dysfunction (Hulsmans *et al.*, 2018). In addition, treatment with the selective CCL2 receptor antagonist, **RS-102895** (Figure 1), attenuated kidney injury in renovascular and AngII-infused hypertensive mice. However, the effects on BP were disappointing (Elmarakby *et al.*, 2007; Kashyap *et al.*, 2016). In fact, the potential role of macrophages on the pathophysiology of hypertension seems to be more related to vascular, renal and neurovascular damage (Justin Rucker and Crowley, 2017) than BP elevation *per se*. On the other hand, antagonism of the chemokine receptor, CCR2, with **INCB3344** reversed DOCA-salt-induced elevations in BP (Chan *et al.*, 2012a), which may be related to the improvement of vascular function. However, neither RS-102895 nor INCB3344 have been tested in humans (Figure 2).

TLR inhibition

Several attempts have been made to inhibit the receptors involved in innate immunity and their downstream pathways by pharmacological interventions (Figure 1). Treatment of SHR (Bomfim *et al.*, 2012) and AngII-infused mice (Hernanz *et al.*, 2015) with neutralizing antibodies to TLR4 (Figure 1) ameliorated vascular dysfunction and lowered BP, presumably by decreasing vascular resistance. Also, anti-TLR4-Ig reversed cardiac hypertrophy (Echem *et al.*, 2015). In SRH, the earlier the anti-TLR-4 treatment starts, the greater is the reduction of BP (Bomfim *et al.*, 2012; Echem *et al.*, 2015). Although we are still far from clinical use of anti-TLR4-Ig, the safety profile of this agent shown in a recent phase I study conducted in 73 healthy volunteers (Monnet *et al.*, 2017) should encourage further clinical trials in hypertensive patients (Figure 2). Although there are data to support TLR4 as a target in hypertension, the TLR4 antagonist, **eritoran**, has not been tested either in experimental models of hypertension or in clinical studies.

In SHR, TLR9 contributes to dysfunctional vascular reactivity and treatment of SHRs with the TLR9 antagonist, ODN2088, lowered BP (McCarthy *et al.*, 2015). Similarly, **chloroquine** caused a significant decrease in BP by inhibiting TLR9 downstream signalling proteins (McCarthy *et al.*, 2017). Chloroquine, which was developed primarily to treat malaria, has anti-inflammatory and immunomodulatory properties, in part related to the inhibition of endosomal TLR9 (Figure 1), allowing its application to the treatment of inflammatory disease (Al-Bari, 2015) and making it an attractive candidate to be tested in hypertension. Nonetheless, the abnormal cardiac conduction disorders and cardiomyopathy related to long-term treatment with
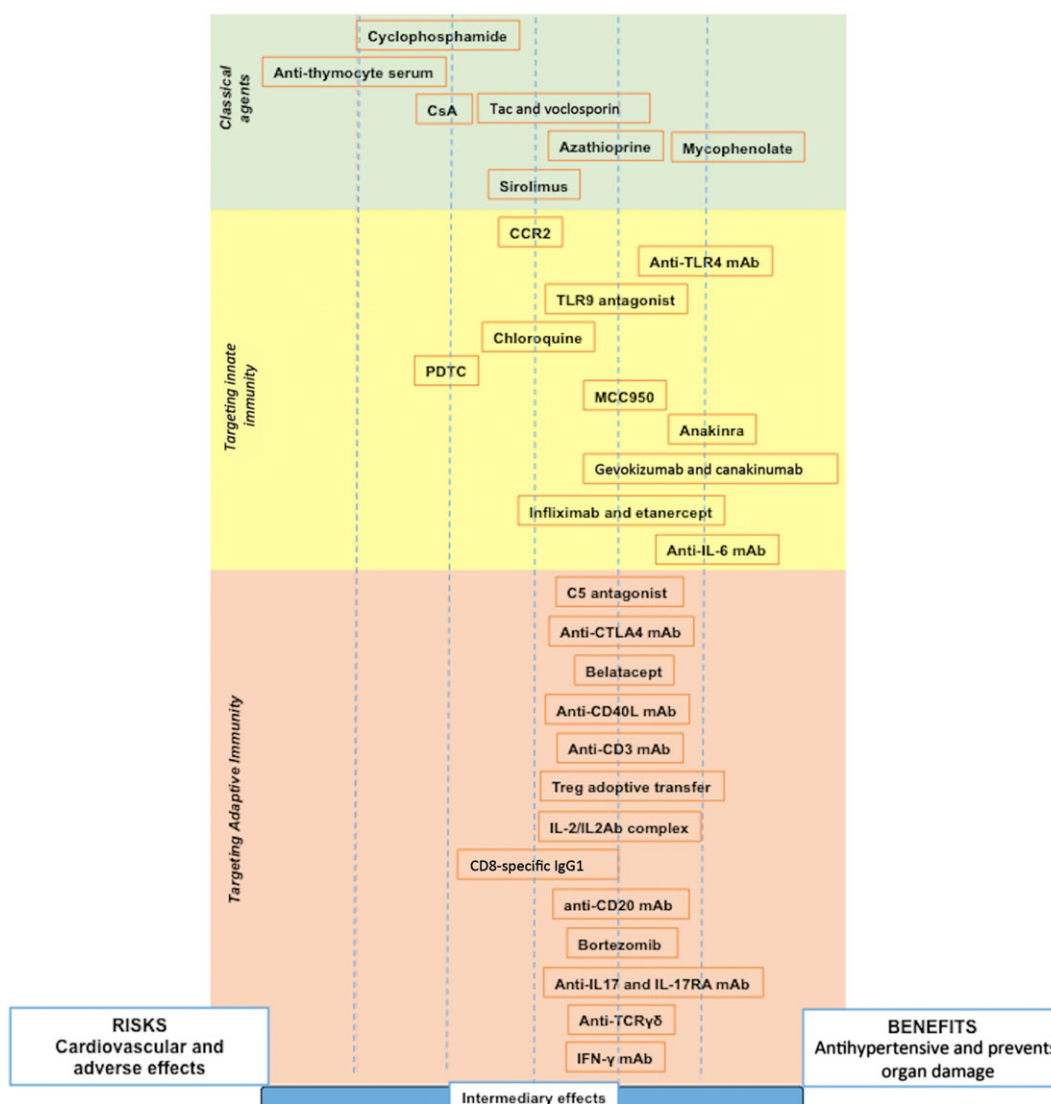
Figure 2

Differential effects of immunosuppressants and immunomodulators on hypertension. Classical immunosuppressant drugs are in the green section, immunomodulators targeting the innate immune response are in the yellow section and immunomodulators targeting the adaptive immune response are in the red section. Drugs shifted to the right have these effects: (i) reduced BP, (ii) decreased organ damage and/or (iii) there is clinical evidence of cardiovascular benefits. Drugs on the left of the figure indicate that one or more of these conditions were met: (i) does not have clinical evidence in hypertension, only experimental; (ii) it works in one hypertensive model and others had no effect and/or (iii) it is toxic to the cardiovascular system. The centre position indicates intermediary effects, with risks and benefits to hypertension. Overall, this figure correlates the risk–benefit ratio to treat hypertension. Anti-IL-17AR, IL 17A receptor antibody; BAS, basiliximab; MMF, mycophenolate mofetil; Tac, tacrolimus.

chloroquine (Al-Bari, 2015) must be disadvantages, particularly in patients with existing cardiovascular disease. As a result, there is limited interest in this drug, in the context of hypertension (Figure 2).

NF-κB inhibition

Activation of the NF-κB pathway is a key component of the stimulation of innate immunity by PRR recognition of PAMPs/DAMPs, which in turn results in the expression of pro-inflammatory mediators including cytokines such as TNF-α and IL-1β, chemokines, adhesion molecules and enzymes. Oxidative stress is also a critical trigger to amplify NF-κB activation, which plays an essential role in the

pathogenesis of chronic inflammatory diseases and hypertension. Antioxidants, such as pyrrolidine dithiocarbamate (PDTC), are the most commonly used compounds for the pharmacological inhibition of NF-κB and this compound is known to exert antihypertensive effects (Rodriguez-Iturbe et al., 2005). PDTC also protected against hypertension-induced vascular and cardiac hypertrophy through a mechanism involving down-regulation of MMP (Cau et al., 2015; Cau et al., 2011). Although it is effective, PDTC safety is still a barrier to clinical studies (Figure 2). Historically, dithiocarbamates have been used as insecticides and fungicides, and to our knowledge, no safety assessments of PDTC in humans have yet been carried out.

NLR inhibition

Hypertension also triggers NLR signalling and activation of NLR induces a complex intracellular signalling structure, the inflammasome, that results in the production of highly pro-inflammatory cytokines: IL-1β and IL-18. Treatment of DOCA-salt hypertensive mice with **MCC950**, an inhibitor of NLRP3 inflammasome oligomerization (Figure 1), significantly reduced systolic BP and renal pro-inflammatory cytokines (Krishnan *et al.*, 2016). However, aged mice with AngII-induced hypertension exhibited enhanced expression of NLRP3 inflammasome components in the kidney but had no hypotensive response to treatment with MCC950 (Dinh *et al.*, 2017). Nevertheless, this is a very novel NLRP3 inflammasome inhibitor and a promising compound. The most commonly used drugs for blocking the inflammasome target one of its products, IL-1β through neutralizing antibodies (nAbs) or the recombinant IL-1β soluble receptor (Figure 1). The relevance of IL-1β to hypertensive heart disease has been supported by studies showing that anti-IL-1β-Ig blocks AngII-induced cardiac hypertrophy with no effects on BP (Wang *et al.*, 2014). Human nAbs for IL-1β, such as **gevokizumab** and **canakinumab**, have been approved for clinical use. Importantly, canakinumab led to significantly lower recurrent cardiovascular events (Shah *et al.*, 2018). Moreover, the injection of gevokizumab in the paraventricular nucleus of DSS rats led to lower BP, heart rate, plasma levels of **noradrenaline** and oxidative stress and restored cytokine balance (Qi *et al.*, 2016). Additionally, **anakinra**, which is a recombinant form of the human IL-1β receptor antagonist (**IL-1Ra**), improved renal function and ameliorated hypertension in AngII-infused (Zhang *et al.*, 2016) and DOCA-salt hypertensive mice (Ling *et al.*, 2017). Anakinra has been an approved drug since 2001 to treat the signs of rheumatoid arthritis, and recent preclinical findings have confirmed its efficacy in cardiovascular disease (Abbate *et al.*, 2013; Van Tassell *et al.*, 2017), making the possible clinical applications of anakinra in hypertension, closer than the other drugs mentioned (Figure 2).

TNF-α and IL-6 inhibition

TNF-α and IL-6 are essential effectors of innate immunity, but they are also involved in the adaptive response. Genetic KO animals for both cytokines have already been tested, and both resulted in reduced inflammation, organ damage and BP in AngII-induced hypertension (Sriramula *et al.*, 2008; Brands *et al.*, 2010). **Infliximab**, a monoclonal antibody (mAb) against TNF-α, and **etanercept**, a soluble recombinant **TNF receptor 2** fusion protein, prevented hypertension in experimental models (Filho *et al.*, 2013; Tran *et al.*, 2009), as summarized in Table 1. The inhibition of IL-6 with a nAb (Table 1) also attenuated hypertension and decreased glomerular inflammation (Hashmat *et al.*, 2016). Regarding efficacy, both TNF-α blockers and IL-6 inhibitor normalized BP in experimental studies by controlling important pathways in the pathophysiology of hypertension. However, clinical studies also have demonstrated that infliximab infusions might result in the cytokine release syndrome, anaphylactic reactions and fever with degranulation of mast cells and basophils (Lichtenstein *et al.*, 2015), whereas the mAb anti-IL6 receptor, **tocilizumab**, did not change cardiovascular

risk or events in rheumatoid patients (Kim *et al.*, 2017). Taken together, these results compromise the risk/benefit balance for both of these immunosuppressant drugs (Figure 2).

Complement system inhibition

Eculizumab, an anti-C5 mAb (Figure 1), has been used for the treatment of paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome (Horiuchi and Tsukamoto, 2016). In a case report, treatment with eculizumab for atypical haemolytic uraemic syndrome attenuated severe hypertension and led to the cessation of dialysis in an infant (Ohta *et al.*, 2015). However, the effects of eculizumab in hypertension, associated or not with autoimmune diseases, still need further assessment (Figure 2). The high cost of eculizumab is one of its disadvantages, as well as increased susceptibility to severe infection from encapsulated bacteria (Wiseman, 2016).

Targeting adaptive immune response

Since the development of highly specific drugs targeting molecules involved in the adaptive immune response, several options to interfere with this type of response in the immune component of hypertension are possible (Table 1), as discussed below.

Agents targeting co-stimulatory molecules

The expression of CD80/CD86 on antigen-presenting cell (APC) is required to interact with **CD28** on the T-cell, reinforcing T-cell activation. Once an effective immune response is established, T-cells express cytotoxic T-lymphocyte-associated protein 4 (CTLA4) on their surface, and a competitive binding occurs to CD80/CD86 to down-regulate T-cell activation. In AngII-induced and DOCA-salt-induced hypertension, the blockade of B7-dependent co-stimulation with CTLA4-Ig decreased BP, T-cell cytokine production, accumulation and, consequently, vascular inflammation (Vinh *et al.*, 2010). **Abatacept** is a CTLA4 human IgG (Figure 1) used to mimic this effect on T-cells and has been approved for the treatment of rheumatoid arthritis. The most common adverse effects in humans include headache, nasopharyngitis, upper respiratory tract infection, gastrointestinal infections and, especially, a higher risk of infections (Bugelski and Martin, 2012). **Belatacept** is a drug more selective as a blocker of T-cell co-stimulation. A clinical study, comparing belatacept with cyclosporine, demonstrated amelioration of central aorta haemodynamics, regardless of the effects on arterial stiffness (Seibert *et al.*, 2014). The absence of major clinical trials limits the use of lymphocyte co-stimulation inhibitors in the treatment of hypertension (Figure 2).

The **CD40** on APC interacts with the ligand of CD40 (**CD40L**) on activated T-cells and leads to up-regulation of CD80/CD86 on APC (Figure 1), amplifying T-cell co-stimulatory signalling (Wiseman, 2016). An anti-CD40L in pre-eclamptic Sprague–Dawley rats reduced hypertension, placental oxidative stress and AngII type 1 receptors (Cornelius *et al.*, 2015). No tests have been performed in other models of hypertension. However, the clinical use of anti-CD40L treatment for autoimmune disorders was

discontinued because of the incidence of thrombotic events and myocardial infarction (Sidiropoulos and Boumpas, 2004).

Anti-T-cell receptor drugs

Muromonab-CD3 (**OKT3**) is an anti-CD3 murine mAb (Figure 1), which recognizes the ε chain of the CD3 on T-cells. The T-cells are unable to respond to an antigen or target cells and are opsonized afterwards. OKT3 has been used for the prevention of allograft rejection in renal, heart and hepatic transplantation (Wiseman, 2016). Mathis et al. (2017) demonstrated that anti-CD3 therapy resulted in attenuation of the development of hypertension in female mice with SLE. The main limitation of OKT3 is the development of the cytokine release syndrome, a condition with symptoms similar to those of severe infection, such as fever and hypotension (Bugelski and Martin, 2012).

The anti-CD25 antibodies, such as **basiliximab** and **daclizumab**, are another example of T-cell blockers (Van Gelder et al., 2004), based on the fundamental role played by IL-2 in lymphocyte proliferation. These drugs bind to the CD25 chain of the IL-2 receptor, preventing IL-2 interaction with its receptor on the surface of T-lymphocytes (Van Gelder et al., 2004). Both are approved drugs for immunosuppressant proposes, but there is little information about their cardiovascular effects. The favourable safety profile of anti-CD25 antibodies enhances the interest of its use for trials in hypertensive patients (Figure 2).

Treg increase

Treg cell therapy has emerged as a strategy to induce tolerance in organ transplantation and autoimmune disease. In hypertension, adoptive transfer of Treg prevents AngII-induced hypertension and vascular injury (Barhoumi et al., 2011) and improves coronary artery endothelial dysfunction (Matrougui et al., 2011). However, the use of Treg adoptive transfer as a therapy in humans may be limited due to the low cell numbers present in donor lymphoid organs, requiring a large number of donors or in vitro expansion.

In another approach, the IL-2/IL-2 antibody complex binds to the small population of CD4$^+$ T-lymphocytes expressing CD25$^-$ and induces in vivo expansion of CD4$^+$CD25$^+$ forkhead box P3$^+$ Treg cells (Webster et al., 2009), as illustrated in Figure 1. Accordingly, IL-2/IL-2 antibody complex induced Treg expansion in AngII-infused mice and decreased vascular stiffness (Majeed et al., 2014) and attenuated the progression of congestive heart in mice after transverse aortic constriction (Wang et al., 2016). Despite this effect, it does not seem to be an appropriate option to control BP, as the IL-2/IL-2Ab complex did not lower the high BP of AngII-infused mice or that of mice with transverse aortic constriction. However, IL-2/IL-2 antibody complex is still an experimental approach.

CD8 T-cell inhibition

Although recent papers have shown the role for CD8 T-cells in hypertension, few studies have assessed the effects of blocking CD8 T-cell activation in this condition. Ma et al. (2014) used WT mice infused with AngII treated with the CD8-specific IgG1 antibody (Figure 1), which caused an efficient depletion of CD8$^+$ T-cells. They found that treatment reduced cardiac profibrogenic inflammation, but they did not measure BP in the treated animals. This study used only CD8 KO mice infused with AngII. According to these findings, CD8 cells have an important role in hypertension. However, any clinical applications will depend on a better knowledge of how to control this cell type.

B-cell targeting

Mature B-cells have a **CD20** antigen expressed on its surface. Hence, anti-CD20 mAbs are useful for the treatment of lymphoproliferative diseases, such as follicular non-Hodgkin's lymphoma and autoimmune haematological disorders (Hansel et al., 2010). The first generation of anti-CD20 mAbs includes **rituximab**, while the second humanized generation has lower immunogenicity and comprises **ofatumumab**, **veltuzumab** and **ocrelizumab** (Wiseman, 2016). Little data of their efficacy against hypertension is available. However, an anti-CD20 (analogous to the clinically used drug) reduced BP in AngII hypertensive mice (Chan et al., 2015). In terms of adverse effects, anti-CD20 Abs are associated with immunosuppression, infections, renal toxicity, cardiac arrhythmias and several other effects (Wiseman, 2016).

Targeting B-cell differentiation is another mechanism of B-cell blockade, which is primarily used in autoimmune diseases and is accomplished by drugs like **belimumab** and **atacicept** (Wiseman, 2016). The principle is to impair the binding of B-cell-activating factors to their receptors, thus inhibiting B-cell maturation (Wiseman, 2016). However, the role of these immunomodulators in the context of hypertension, associated or not with SLE, still needs further investigation, as their use has been limited in autoimmune diseases.

The ubiquitin–proteasome system controls protein turnover, and its inhibition induces apoptosis, particularly in effector B-cells (Wiseman, 2016). The proteasome inhibitors PSI and **MG132** demonstrated antihypertensive effects and suppression of hypertension-induced cardiac fibrosis, respectively (Takaoka et al., 1998; Meiners et al., 2004), but, in both cases, their effects on B-cell activity were not addressed. **Bortezomib** (Figure 1), a proteasome inhibitor approved for the treatment of multiple myeloma, attenuated BP increase and aortic vascular remodelling in AngII-infused mice (Li et al., 2013). Also, recent data on a rat model of SLE demonstrated significant reduction on BP and improvement of renal function by bortezomib, and these effects were associated with the bortezomib-induced decrease of plasma immunoglobulin levels and B-cell and T-cell infiltration in the kidneys (Taylor et al., 2018a). Although bortezomib emerges as a modulator of the adaptive immune responses driven by B-cells and T-cells in hypertension, common adverse effects in patients with myeloma include dose-limiting toxicity leading to sensory neuropathy, asthenic conditions, gastrointestinal disorders and no dose-limiting responses such as thrombocytopenia and anaemia (Bross et al., 2004). For all the reasons discussed above, anti-B-cell drugs have a risk/benefit balance, limiting their use in hypertension (Figure 2).

IL-17 inhibition

The response of Th17 and γδ T-cells in producing IL-17 has gained importance in hypertension. For example, both T-cell receptor (TCR) δ gene deletion and treatment with anti-TCRγδ

(Figure 1) blunted endothelial dysfunction and hypertension in AngII-infused mice (Caillon *et al.*, 2017). It has been suggested that IL-17 plays a fundamental role in these effects. In addition, direct inhibition of IL-17 with Ab therapy (IL-17 nAb; IL-17A mAb) or the soluble specific receptor for IL-17, attenuated hypertension in different experimental models (Cornelius *et al.*, 2013; Saleh *et al.*, 2016; Chiasson *et al.*, 2017). The mechanisms involved in hypertension control induced by direct inhibitors of IL-17 seem to include the enhancement of Treg cells in spleen and lymph node, reduction of renal and vascular infiltration of total T-cells (CD3$^+$), Th17 and T-cytotoxic (CD8$^+$). Also, IL-17 inhibition provides a decrease in TGF-β, ROS, albuminuria, organ damage and vascular dysfunction (Cornelius *et al.*, 2013; Saleh *et al.*, 2016; Chiasson *et al.*, 2017). Similarly, inhibition, using IL-17A receptor mAb, attenuated hypertension, albuminuria, renal and aortic infiltration of total leukocytes, total T-cell (CD3$^+$), T-cell (CD4$^+$), T-cytotoxic (CD8$^+$), renal TGF-β and organ damage (Saleh *et al.*, 2016). In normotensive patients, IL-17RA mAb therapy showed an acceptable cardiovascular safety (Papp *et al.*, 2016). However, IL-17 seems to play a protective role in renal disease (Mohamed *et al.*, 2016), and its inhibition could accelerate renal injury in specific cases of hypertension (Krebs *et al.*, 2014). Therefore, although IL-17 is not the only cytokine involved on the pathophysiology of hypertension, it has the potential to be one of the targets for the treatment of hypertension, by immunosuppressant drugs in the future.

IFN-γ inhibition

Although there is little evidence relating to the pharmacological inhibition of IFN in hypertension, it is important to mention that anti-IFN therapy might play an important role in combination with other drugs. IFN is a cytokine involved in Th1 cell differentiation. Although IFN-γ receptor KO mice did not display an antihypertensive effect in the model of AngII-induced hypertension, they did show reduced cardiac macrophages and T-cell infiltration, fibrosis and hypertrophy, demonstrating cardioprotective effects (Marko *et al.*, 2012). Moreover, inhibition of IFN-γ (Figure 1) was able to partly prevent the elevation of BP in mice overexpressing the MR after AngII infusion. These results suggest that IFN-γ participates in the pathophysiology of AngII-induced hypertension, but it is not the sole factor responsible for BP elevation (Sun *et al.*, 2017). Considering these data together, patients may benefit from the combination of IFN-γ inhibition with other drugs, as a therapeutic strategy to treat hypertension. Nevertheless, studies are warranted to test this hypothesis.

Conclusion

The recognition that hypertensive disease is accompanied by DAMPs and formation and release of neoantigens, which trigger a sophisticated immune response, has opened a new clinical approach to the treatment of hypertension. The most recent efforts made to determine the involvement of innate and adaptive immunity in hypertension were conducted in KO animals. From a pharmacological standpoint, new strategies to treat hypertension are evolving with the explosion of knowledge about the role of the activation of the immune system, in this condition. As an example, immunosuppressant drugs have been tested in animal models of hypertension, and some clinical information is now available about their cardiovascular safety. Also, the present review has outlined advantages and disadvantages of therapy with classical immunosuppressant drugs and newer targeted therapies that block specific steps of the activation of the immune system, some of which are still in the development phase. Current findings in the literature show a more favourable risk/benefit ratio profile of targeted therapies over classical immunosuppressant drugs, which may decrease BP and protect hypertensive patients from end-organ damage. In order to implement this challenging clinical translation, we would first propose that more clinical trials evaluating hypertension as an outcome are needed. Secondly, a careful risk–benefit evaluation should be performed before therapy, considering human data about drug safety and efficacy to reduce BP or other cardiovascular damage (Figure 2). The translation of this knowledge, from experimental science to clinical practice, starts with the right choice of the immunomodulator based on the patient's markers of inflammation and with appropriate selection of the patients. Also, there must be caution in interpreting the published results, as the majority of studies correlating activation of the immune system with the development and maintenance of hypertension were carried out in AngII-infused animals. To our knowledge, no studies have addressed or compared the relevance of all these findings across different hypertensive models. It is possible that contrasting results from different hypertensive conditions may reflect particular inflammatory pathways that are not relevant in all other models. Thus, studies comparing the activation profile of the immune system across different hypertensive models and also with human hypertensive patients may provide insights into the mechanisms triggered in each model. Also, it may allow the development of therapies more likely to translate into human studies.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding *et al.*, 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander *et al.*, 2017a,b,c,d,e).

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Conflict of interest

The authors declare no conflicts of interest.

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