Targeting the immune system to treat hypertension: where are we?

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Purpose of review
Research over the past decade has significantly deepened our understanding of mechanisms that drive the development of hypertension. In particular, a novel paradigm of inflammation as a common mediator of cardiovascular and kidney disease has emerged. This review will summarize the role of the immune system in cardiovascular disease, explore some of the most promising new therapeutic directions and consider their potential as new treatments for hypertension.

Recent findings
Recent data continue to demonstrate that targeting the immune system can prevent hypertension in a variety of experimental models. Tempering the enthusiasm for a long-awaited new approach to treating hypertension is decades of clinical data, showing that classic immunosuppression regimens are associated with significant side-effects – including cardiovascular disease – that effectively preclude their use in the setting of chronic hypertension. New, more specific therapies are being developed that target cytokines including IL-17, IL-6 and TNFα.

Summary
Preclinical data convincingly demonstrate a key role for the immune system and specific cytokine mediators. Several biotherapeutics targeting these pathways are on the market and more are in development. Side-effects, however, continue to resemble those of classic immunosuppressants, highlighting the challenge of translating these research advances into new therapies for hypertension.

Video abstract
http://links.lww.com/CONH/A9

Keywords
anti-IL-17, anti-TNFα, calcineurin inhibitors, cardiovascular disease, hypertension, immunosuppression, inflammation

INTRODUCTION

Hypertension is a systemic disorder that affects over 50 million people in the United States. Despite advances in treatments, many individuals continue to have uncontrolled hypertension, putting them at increased risk of stroke, ischemic heart disease and other complications. Hypertension is a systemic disease characterized by increased vascular resistance and multiorgan derangements. However, the pathogenesis is incompletely understood. The central role of the vasculature is evident in the success of the most common therapies including angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers which work by inducing vasodilation and decreasing vascular resistance. But, in addition to the vasculature, the kidney and central nervous system (CNS) are well established in both the cause and disease of hypertension. Genetic mutations that alter salt handling by the distal nephron commonly induce hypertension [1]. Moreover, abrogating renal sympathetic nerve activation with renal denervation lowers blood pressure (BP) in both animals and humans [2,3]. Finally, angiotensin II (AngII) acts directly on the brain and increases sympathetic outflow, thereby increasing BP (recently reviewed in [4]). Although the immune system has long been recognized as a factor in hypertension and

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Curr Opin Nephrol Hypertens 2014, 23:473–479
DOI:10.1097/MNH.0000000000000052

KEY POINTS

- Systemic inflammation alters vascular and renal function and contributes to hypertension.
- Key factors that drive the inflammatory cascade include IL-17, IL-6 and TNFα.
- Classic immunosuppressant drugs are associated with a range of side-effects including infections and, in many cases, hypertension and cardiovascular disease.
- New biopharmaceuticals that target IL-17 and other cytokines hold promise, but significant side-effects may complicate the use of these agents for hypertension.

cardiovascular disease, recent work has convincingly established chronic inflammation as a common disease in the vasculature, kidney and CNS. The key players in these events are, therefore, compelling new targets for therapeutic intervention.

INFLAMMATION AS A DRIVER OF RENAL DISEASE AND HYPERTENSION

Work in the last decade has shown that classic models of AngII and high salt-mediated hypertension are associated with vascular accumulation of a host of immune cells, including T cells, B cells, monocytes, macrophages and dendritic cells [5]. Infiltration of these cells increases production of reactive oxygen species (ROS) that contribute to endothelial cell dysfunction [6] and reduce vessel wall stretch [7]. Similarly, AngII and high salt-induced hypertension induces infiltration of T cells into the kidney [8,9] in which the immune cells produce renin and ACE, highlighting that inflammation results in a local potentiation of systemic effects [9,10].

Initiation of inflammation and pathological remodeling is likely rooted in activation of the innate immune system in the form of resident monocytes. In addition, several groups have identified macrophages as key mediators of AngII-induced vascular inflammation and hypertension. For example, mice lacking macrophage colony stimulating factor have reduced macrophages and attenuated vascular inflammation, oxidative stress and inflammation in response to AngII [11]. Moreover, Cre recombinase-driven expression of the diphtheria toxin receptor in LysM cells attenuated vascular macrophage and neutrophil infiltration and hypertension [12]. Adoptive transfer of macrophages, but not neutrophils, restored AngII-mediated effects. Macrophages are prolific producers of ROS and other cytokines which can have local and systemic effects. One important role may be as a link between tissue-level changes and systemic responses to hypertensive agents via activation of the adaptive immune system. Recombinant activating gene 1 (*Rag1*) -/- mice and severe combined immunodeficiency (SCID) mice have been particularly useful in identifying the role of the adaptive immune system in hypertension. Guzik *et al.* [13] showed that Rag-/- mice are protected from AngII and desoxycorticosterone acetate (DOCA)-salt-mediated vascular inflammation and hypertension. Adoptive transfer of T cells, but not B cells, restores AngII-mediated disease [13], convincingly demonstrating the role of the T cells in this pathological cascade. Similar mechanisms were reported by Crowley *et al.* [14] in the SCID model and by Mattson *et al.* [15] in zinc finger nuclease-mediated rag knockout rats. More specifically, Vinh *et al.* [16] showed that mice lacking the B7 ligand on antigen-presenting cells which cannot stimulate T cells are protected from AngII and DOCA-mediated vascular inflammation and hypertension. Finally, programing of the innate immune system by hypertension has been elegantly demonstrated by several classic studies. Okuda and Grollman [17] reported in 1967 that autoimmune hypertension can be induced in recipient rats following transfer of lymph nodes from hypertensive animals. In 1981, Olsen [18] similarly reported that transfer of splenic cells from hypertensive rats to normotensive donors induced hypertension, inflammation and vascular wall thickening [18]. Viewed in light of recent advances, these historical studies provide a link to functional changes in programing of the adaptive immune system by hypertensive agents.

These studies and others like them define a primary role for the innate immune system via macrophages (and possibly other dendritic cells) that produce cytokines and abundant ROS in response to hypertension. These signals then activate adaptive immune cells – primarily T cells – which compound the local production of ROS and cytokines and also communicate the immune response to other organs (Fig. 1). The systemic derangements include aberrant sympathetic stimulation, enhanced cytokine production, recruitment of immune cells into vessel walls, the kidney and the brain, activation of adhesion molecules, and elevated oxidative stress. Although it remains a working model, this schema points toward new therapeutic strategies for hypertension: targeting the immune system.

TARGETING THE IMMUNE SYSTEM: CLASSIC APPROACHES

Experimental data make a compelling case for targeting the immune system as a new therapeutic

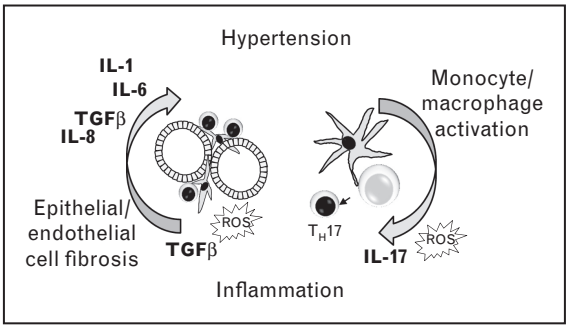

FIGURE 1. Paradigm of inflammation and immune cell activation in hypertension. Hypertension and inflammation active overlapping and synergistic pathways to induce vascular resistance and organ damage. Monocyte/macrophage activation is a key player in the induction of T_H17 cells and IL-17 production. Infiltration of immune cells then leads to additional cytokine and ROS production which act on epithelial and endothelial cells of the kidney and vessels. The resulting cell injury likewise stimulates further cytokine production and potentiates systemic inflammation and hypertension.

approach to hypertension. Immune suppression has been used in a variety of clinical settings, including postorgan transplantation and autoimmune diseases, for several decades, providing the opportunity to examine the potential for applying this approach to hypertension. Clinical immune suppression took a giant leap forward in the early 1980s with the discovery of cyclosporine, a calcineurin inhibitor (CNI), and, shortly after, the related compound tacrolimus [19▪]. Precyclosporine, most immunosuppression regimens consisted of azathioprine, a nucleoside analog and corticosteroids. The addition of CNIs lessened the need for azathioprine, although most patients still take mycophenylate mofitil (MMF) and steroids in addition to cyclosporine or tacrolimus. The success of CNIs at preventing organ rejection eventually led to a greater awareness of consequences of the aggressive therapies as patients survived longer but developed consistent side-effects. In particular, hypertension, which was seen in less than half of transplant patients before CNIs, currently affects 70–90% of patients [20]. Moreover, cardiovascular diseases, including ischemic heart disease and vascular dysfunction, are the leading cause of death of transplant patients [21]. These facts lead to important questions as the possibility of targeting the immune system is considered a treatment for hypertension. It is helpful to further explore the mechanism and side-effects of each class of immunosuppressants.

CNIs target the enzyme calcineurin, a ubiquitously expressed, calcium-dependent phosphatase. Calcineurin is involved in T-cell-mediated signaling and regulates expression of cytokines through the transcription factor Nuclear Factor of Activated T Cells (NFAT) [22]. NFAT and its family members (NFATc1-c5) are also widely expressed. Common side-effects of CNIs include renal fibrosis, diabetes, skin cancer and hypertension [23–25]. Knockout mouse models of calcineurin indicate that these effects can be directly linked to calcineurin action in the kidney and other organs [26–29]. Despite the established link between chronic CNI use and hypertension, there is at least one study that tested the effect of tacrolimus (which is associated with less nephrotoxicity than cyclosporine) in an experimental model of hypertension. A 3-week course of tacrolimus was reported to reduce salt-sensitive hypertension and renal oxidative stress in Dahl salt-sensitive rats [9]. Although the data suggest that CNIs may have some efficacy toward reducing hypertension in animal models, the well-established side-effects make this class of drug an unreasonable approach to hypertension.

Corticosteroids are a frequent part of many immunosuppression regimens. The synthetic hormones interact with the glucocorticoid receptor and then alter gene transcription. Although widely used, glucocorticoids are associated with a number of significant side-effects, including insulin resistance and diabetes, increased susceptibility to infection, skeletal muscle atrophy and hypertension. Anti-inflammatory actions are thought to be due to transrepression of gene targets, including cytokines, whereas metabolic actions are due to activation of a different group of target genes [30]. Although there is interest in developing modified synthetic versions of the steroid that separate desirable immune suppression from many of the undesirable effects including hypertension [30], it is unclear if the approach would lead to a compound with a toxicity profile suited to chronic control of essential hypertension.

In contrast to CNIs and corticosteroids, MMF is not associated with hypertension in patients or animal models. MMF is metabolized to mycophenolic acid (MFA) which inhibits inosine monophosphate dehydrogenase (IMPDH), an enzyme required for synthesis of guanosine by T and B cells [31]. Inhibition of IMPDH blocks T and B cell proliferation and may also induce apoptosis of activated T lymphocytes [32]. MMF has a five-fold increased affinity for IMPDH type II which is expressed by T and B cells as opposed to type I which is expressed by most other cells. MMF is associated with generally mild side-effects including gastrointestinal symptoms and leukopenia although it is contraindicated during pregnancy [33]. Long-term use of MMF may be associated with an increased risk

of infection, lymphoma and other neoplasias, but the data are inconclusive as to the risk that should be attributed to MMF as it is virtually always given in combination with other drugs. Animal models support the efficacy of MMF for hypertension. Boesen *et al*. and de Miguel *et al*. showed in two different rat models that MMF abrogates renal damage and lowers BP [10,34,35▪]. Similar findings were previously reported [36–38]. The effect of MMF on hypertension in humans has been at least tangentially examined. Herrera *et al*. [39] reported in 2006 that MMF treatment was associated with reduced hypertension in a cohort of individuals with essential hypertension that were being treated with MMF for either rheumatoid arthritis or psoriasis. Of the most frequently used immunosuppression agents, MMF has the most potential for use in the setting of hypertension. Animal models and limited clinical data support the feasibility of its use. However, it remains unclear if MMF offers sufficient benefits to offset a side-effect profile that still far exceeds current antihypertensive medications.

TARGETING THE IMMUNE SYSTEM: NEW APPROACHES

The relatively fewer side-effects associated with MMF compared with CNIs highlight the importance of increased specificity when considering approaches to targeting the immune system. In addition to uncovering the interaction between the immune system and hypertension, significant advances have been made in identifying specific cytokines that mediate inflammation, oxidative stress and organ damage. In particular, the proinflammatory cytokines IL-17, IL-1, IL-12, IL-8, IL-6 and TNFα are likely to be involved in the induction or pathological response to hypertension. Of these, there is considerable interest in IL-17. IL-17 cytokines include six family members (IL-17A-F) and their ubiquitous receptors. IL-17A is the prototypic molecule; its expression identifies a unique subset of CD4+ T cells now known as T_H17 cells. In addition to T_H17 cells, IL-17 is produced by dendritic cells, macrophages and natural killer cells [40,41]. IL-17 production is driven by IL-6 and IL-1β [42] and is indirectly enhanced by IFNγ and TGFβ-mediated suppression of T_H1 cells which increases T_H17 cells. IL-17, in turn, mediates production of TNFα, IL-1, IL-6 and IL-8, which are linked to hypertension and tissue damage [43] (Fig. 2).

Elevated production of IL-17 is associated with autoimmune diseases in both animal models and humans (recently reviewed in [44]). In addition, IL-17 is increased in hypertension and related diseases, including preeclampsia and lupus [45–47].

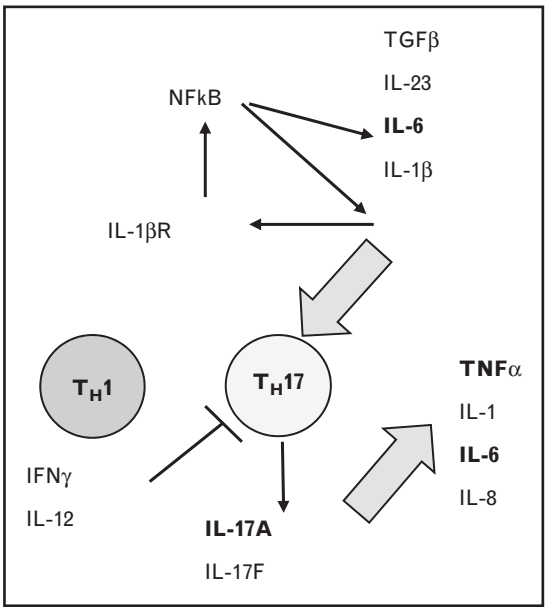

FIGURE 2. Key cytokines involved in the induction and effects of IL-17. IL-17 is emerging as a central pathway in inflammatory diseases including hypertension. T_H17 cells are generated in response to a range of cytokines, including TGFβ, IL-23, IL-6 and IL-1β. Cytokine production is potentiated by local interaction with IL-1βR and downstream activation of the transcription factor NFkB. IL-17 is produced by T_H17 cells (and other immune cells) and indirectly by factors that reduce the proportion of T_H1 T cells. Current targets of biopharmaceutical development are bolded and include IL-6, TNFα and IL-17A.

Expression of the multifunctional proinflammatory IL-6, which plays a critical role in expression and production of IL-17, correlates with changes in BP in patients with hypertension [48,49]. Moreover, accumulation of IL-6 in the kidney is associated with Ang-II-mediated hypertension in patients with chronic kidney disease and hypertension [50,51]. Downstream of IL-17, TNFα expression is closely identified with inflammatory autoimmune diseases, including rheumatoid arthritis and psoriasis. In addition, TNFα may also be increased with hypertension [49,52]. Taken together, these data suggest that targeting the IL-17 pathway may be beneficial in hypertension. A growing body of preclinical data supports this model. First, infusion of IL-17 in mice is sufficient to cause hypertension [53]. Conversely, mice lacking IL-17 are resistant to angiotensin II-mediated hypertension and develop less vascular remodeling and oxidative stress than wildtype mice [54]. Finally, lentiviral targeting of IL-17R improves cardiac function and decreases fibrosis in the spontaneously hypertensive rat model [55]. Similar promising results have been reported using IL-6 knockout mice [56] and

Table 1. Summary of new therapeutic targets for hypertension

Biopharmaceutical	Target	Phase	Side-effects
Etanercept	TNFα	Market (Embril)	Infections, possible increase in malignancies
Infliximab	TNFα	Market (Remicade)	
Certolizumab pegol	TNFα	Market (Cimzia)	
Golimumab	TNFα	Market (Simponi)	
Adalimumab	TNFαR	Market (Humera)	Infections, possible increase in malignancies
Ixekizumab	IL-17A	Phase 3	Limited data; Infection, neutropenia
Secukinumab	IL-17A	Phase 2/3	
Brodalumab	IL-17R	Phase 3	Limited data
Sirukumab	IL-6	Phase 3	Limited data
Sarilumab	IL-6R	Phase 3	Limited data
Tocilizumab	IL-6R	Market (Actemra)	Infections, neutropenia, hepatotoxicity
Gevokizumab	IL-1β	Phase 3	Limited data
Anakinra	IL-1R	Market (Kineret)	Infection, neutropenia, possible malignancies
Tildrakizumab	IL-23	Phase 3	Limited data
Ustekinumab	IL-12/23	Market (Stelara)	Infection, possible malignancies

treatment of rodent models with an anti-TNFα antibody [57,58].

The recent preclinical data supporting targeting the IL-17 pathway for the treatment of hypertension have not yet been translated to clinical studies. However, because of its established role in autoimmunity, IL-17 is the subject of great interest in the fields of rheumatoid arthritis and psoriasis and several biopharmaceuticals are in development to target IL-17 production and action (summarized in Table 1). TNFα inhibitors are the farthest in development and five different drugs have been approved by the Food and Drug Administration. These include a recombinant TNFα receptor fusion protein, entanercept (Enbrel) and four monoclonal antibodies to TNFα including adalimumab (Humira). As a class, anti-TNFα biopharmaceuticals have significant side-effects including infections and, potentially, an increased risk of cancer [59]. Although it has not been studied directly, the data do suggest a potential cardiovascular benefit for individuals on anti-TNFα therapies. Hugh *et al*. reported in a recent literature overview that use of anti-TNFα therapies is associated with reduced cardiovascular events in psoriasis patients [60▪]. Interestingly, several trials are currently recruiting that will look at the effectiveness of anti-TNFα biopharmaceuticals in patients with psoriasis and a comorbid condition including hypertension. It remains to be seen, however, if cardiovascular benefits outweigh side-effects including the increased risk of infection.

Other biopharmaceutics targeting IL-17 currently in development include monoclonal antibodies against IL-17A or IL-17 receptor. Ixekizumab, secukinumab and brodalumab are in phase 3 trials for psoriasis or rheumatoid arthritis. A summary of phase 2 data was recently published confirming a beneficial effect of targeting IL-17 for psoriasis and suggesting a tolerable safety profile. The major adverse effects were upper respiratory infections, nasopharyngitis and transient neutropenia [61▪]. An IL-6 monoclonal antibody, sirukumab, is also in phase 3 clinical trials. Phase 1 and 2 data indicate that infections, neutropenia and a dose-dependent decrease in white blood cells are common adverse events [62]. Finally, other strategies to target IL-17 include small molecule inhibitors of retinoic acid-related orphan receptor γt (RORγt), which is a master regulator of T_H17 cell development [63]. Although promising, the efficacy of these agents in hypertension remains to be established.

CONCLUSION

Emerging evidence supports the immune system as a new therapeutic target for the treatment of hypertension and, potentially, other cardiovascular and renal diseases. Decades of clinical experience with potent immunosuppressants including CNIs highlight the challenges of inhibiting the immune system while preserving a tolerable safety profile. This is especially relevant in the setting of hypertension which affects millions of otherwise generally healthy adults and for which there are currently well tolerated, safe therapies. Research into the mechanisms of inflammatory hypertension has identified a group of promising cytokine targets. With the success of Enbrel and Humira, biopharmaceuticals are a fast growing segment of the pharmaceutical industry. Limited clinical data support the

cardiovascular benefits of these therapeutic options, but the efficacy of treating essential hypertension has yet to be directly tested. Moreover, it remains to be seen if targeting these immune mediators can provide superior benefits to the current standards of renal and cardiovascular care with an acceptable safety profile.

Acknowledgements

The authors wish to acknowledge M. Gumz, J. Kocerha and C. Williams for helpful discussion and editing of the manuscript. Funding was provided by the Philadelphia College of Osteopathic Medicine Chief Science Office.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. Cell 2001; 104:545–556.
2. Esler MD, Krum H, Sobotka PA, *et al.* Symplicity HTN-2 Investigators. Renal sympathetic denervation in patients with treatment-resistant hypertension (the symplicity HTN-2 trial): a randomised controlled trial. Lancet 2010; 376:1903–1909.
3. DiBona GF, Esler M. Translational medicine: the antihypertensive effect of renal denervation. Am J Physiol Regul Integr Comp Physiol 2010; 298:R245–R253.
4. Ramchandra R, Yao ST, May CN. Organ selective regulation of sympathetic outflow by the brain angiotensin system. Curr Hypertens Rep 2013; 15:401–408.
5. Trott DW, Harrison DG. The immune system in hypertension. Adv Physiol Educ 2014; 38:20–24.
6. Dikalov SI, Nazarewicz RR, Bikineyeva A, *et al.* Nox2-induced production of mitochondrial superoxide in angiotensin II-mediated endothelial oxidative stress and hypertension. Antioxid Redox Signal 2014; 20:281–294.
7. Wu J, Thabet SR, Kirabo A, *et al.* Inflammation and mechanical stretch promote aortic stiffening in hypertension through activation of p38 mitogen-activated protein kinase. Circ Res 2014; 114:616–625.
8. Ozawa Y, Kobori H, Suzaki Y, Navar LG. Sustained renal interstitial macrophage infiltration following chronic angiotensin II infusions. Am J Physiol Renal Physiol 2007; 292:F330–F339.
9. De Miguel C, Guo C, Lund H, *et al.* Infiltrating T lymphocytes in the kidney increase oxidative stress and participate in the development of hypertension and renal disease. Am J Physiol Renal Physiol 2011; 300:F734–F742.
10. De Miguel C, Das S, Lund H, Mattson DL. T lymphocytes mediate hypertension and kidney damage in Dahl salt-sensitive rats. Am J Physiol Regul Integr Comp Physiol V 298 2010; R1136–R1142.
11. De Ciuceis C, Amiri F, Brassard P, *et al.* Reduced vascular remodeling, endothelial dysfunction, and oxidative stress in resistance arteries of angiotensin II-infused macrophage colony-stimulating factor-deficient mice: evidence for a role in inflammation in angiotensin-induced vascular injury. Arterioscler Thromb Vasc Biol 2005; 25:2106–2113.
12. Wenzel P, Knorr M, Kossmann S, *et al.* Lysozyme M-positive monocytes mediate angiotensin II-induced arterial hypertension and vascular dysfunction. Circulation 2011; 124:1370–1381.
13. Guzik TJ, Hoch NE, Brown KA, *et al.* Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. J Exp Med 2007; 204:2449–2460.
14. Crowley SD, Song YS, Lin EE, *et al.* Lymphocyte responses exacerbate angiotensin II-dependent hypertension. Am J Physiol Regul Integr Comp Physiol 2010; 298:R1089–R1097.
15. Mattson DL, Lund H, Guo C, *et al.* Genetic mutation of recombination activating gene 1 in Dahl salt-sensitive rats attenuates hypertension and renal damage. Am J Physiol Regul Integr Comp Physiol 2013; 304:R407–R414.
16. Vinh A, Chen W, Blinder Y, *et al.* Inhibition and genetic ablation of the B7/CD28 T-cell costimulation axis prevents experimental hypertension. Circulation 2010; 122:2529–2537.
17. Okuda T, Grollman A. Passive transfer of autoimmune induced hypertension in the rat by lymph node cells. Tex Rep Biol Med 1967; 25:257–264.
18. Olsen F. Transfer of arterial hypertension by splenic cells from DOCA-salt hypertensive and renal hypertensive rats to normotensive recipients. Acta Pathol Microbiol Scand C 1980; 88:1–5.
19. ■ Azzi JR, Sayegh MH, Mallat SG. Calcineurin inhibitors: 40 years later, can't live without. J Immunol 2013; 191:5785–5791.

This is a recent overview of the history and use of CNIs, including their most common side-effects and current strategies to mitigate or eliminate the drugs. The authors included information about the early attempts to use CNIs for the treatment of rheumatoid arthritis and psoriasis, an interesting parallel to the current development of anti-IL-17 biopharmaceuticals.

20. Taler SJ, Textor SC, Canzanello VJ, Schwartz L. Cyclosporin-induced hypertension: incidence, pathogenesis and management. Drug Saf 1999; 20:437–449.
21. Ojo AO. Cardiovascular complications after renal transplantation and their prevention. Transplantation 2006; 82:603–611.
22. Rusnak F, Mertz P. Calcineurin: form and function. Physiol Rev 2000; 80:1483–1521.
23. Cattaneo D, Perico N, Gaspari F, Remuzzi G. Nephrotoxic aspects of cyclosporine. Transplant Proc 2004; 36 (Suppl 2):234S–239S.
24. Su Q, Weber L, Le Hir M, *et al.* Nephrotoxicity of cyclosporin A and FK506: inhibition of calcineurin phosphatase. Ren Physiol Biochem 1995; 18:128–139.
25. Roullet JB, Xue H, McCarron DA, *et al.* Vascular mechanisms of cyclosporin-induced hypertension in the rat. J Clin Invest 1994; 93:2244–2250.
26. Gooch JL. An emerging role for calcineurin Aalpha in the development and function of the kidney. Am J Physiol Renal Physiol 2006; 290:F769–F776.
27. Gooch JL, Guler RL, Barnes JL, Toro JJ. Loss of calcineurin Aalpha results in altered trafficking of AQP2 and in nephrogenic diabetes insipidus. J Cell Sci 2006; 119 (Pt 12):2468–2476.
28. Gooch JL, Roberts BR, Cobbs SL, Tumlin JA. Loss of the alpha-isoform of calcineurin is sufficient to induce nephrotoxicity and altered expression of transforming growth factor-beta. Transplantation 2007; 83:439–447.
29. Pena JA, Losi-Sasaki JL, Gooch JL. Loss of calcineurin Aalpha alters keratinocyte survival and differentiation. J Invest Dermatol 2010; 130:135–140.
30. Van Raalte DH, Diamant M. Steroid diabetes: from mechanism to treatment? Neth J Med 2014; 72:62–72.
31. Allison AC. Mechanisms of action of mycophenolate mofetil. Lupus 2005; 14 (Suppl 1):s2–8.
32. Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action. Immunopharmacology 2000; 47:85–118.
33. Behrend M. Adverse gastrointestinal effects of mycophenolate mofetil: aetiology, incidence and management. Drug Saf 2001; 24:645–663.
34. Boesen EI, Williams DL, Pollock JS, Pollock DM. Immunosuppression with mycophenolate mofetil attenuates the development of hypertension and albuminuria in deoxycorticosterone acetate-salt hypertensive rats. Clin Exp Pharmacol Physiol 2010; 37:1016–1022.
35. ■ Spradley FT, De Miguel C, Hobbs J, *et al.* Mycophenolate mofetil prevents high-fat diet-induced hypertension and renal glomerular injury in Dahl SS rats. Physiol Rep 2013; 1:e00137. doi: 10.1002/phy2.137. [Epub ahead of print]

This publication is the newest in a decade-long line of work showing that immune suppression by MMF reduces hypertension in animal models.

36. Tian N, Gu JW, Jordan S, *et al.* Immune suppression prevents renal damage and dysfunction and reduces arterial pressure in salt-sensitive hypertension. Am J Physiol Heart Circ Physiol 2007; 292:H1018–H1025.
37. Mattson DL, James L, Berdan EA, Meister CJ. Immune suppression attenuates hypertension and renal disease in the Dahl salt-sensitive rat. Hypertension 2006; 48:149–156.
38. Rodriguez-Iturbe B, Quiroz Y, Herrera-Acosta J, *et al.* The role of immune cells infiltrating the kidney in the pathogenesis of salt-sensitive hypertension. J Hypertens Suppl 2002; 20:S9–S14.
39. Herrera J, Ferrebuz A, MacGregor EG, Rodriguez-Iturbe B. Mycophenolate mofetil treatment improves hypertension in patients with psoriasis and rheumatoid arthritis. J Am Soc Nephrol 2006; 17 (12 Suppl 3):S218–S225.
40. Annunziato F, Cosmi L, Liotta F, *et al.* The phenotype of human Th17 cells and their precursors, the cytokines that mediate their differentiation and the role of Th17 cells in inflammation. Int Immunol 2008; 20:1361–1368.
41. Romagnani S. Human Th17 cells. Arthritis Res Ther 2008; 10:206–213.
42. Nishimoto N. Interleukin-6 as a therapeutic target in candidate inflammatory diseases. Clin Pharmacol Ther 2010; 87:483–487.
43. Matsumoto K, Fukuda N, Abe M, Fujita T. Dendritic cells and macrophages in kidney disease. Clin Exp Nephrol 2010; 14:1–11.
44. Qu N, Xu M, Mizoguchi I, *et al.* Pivotal roles of T-helper 17-related cytokines, IL-17, IL-22, and IL-23, in inflammatory diseases. Clin Dev Immunol 2013; 2013:968549.
45. Wallace K, Morris R, Kyle PB, *et al.* Hypertension, inflammation and T lymphocytes are increased in a rat model of HELLP syndrome. Hypertens Pregnancy 2014; 33:41–54.
46. Lozovoy MA, Simao AN, Morimoto HK, *et al.* Hypertension is associated with serologically active disease in patients with systemic lupus erythematosus: role of increased Th1/Th2 ratio and oxidative stress. Scand J Rheumatol 2014; 43:59–62.
47. Eid RE, Rao DA, Zhou J, *et al.* Interleukin-17 and interferon-gamma are produced concomitantly by human coronary artery-infiltrating T cells and act synergistically on vascular smooth muscle cells. Circulation 2009; 119:1424–1432.

48. Fernandez-Real JM, Vayreda M, Richart C, *et al.* Circulating interleukin 6 levels, blood pressure, and insulin sensitivity in apparently healthy men and women. J Clin Endocrinol Metab 2001; 86:1154–1159.

49. Chae CU, Lee RT, Rifai N, Ridker PM. Blood pressure and inflammation in apparently healthy men. Hypertension 2001; 38:399–403.

50. Zhang W, Wang W, Yu H, *et al.* Interleukin 6 underlies angiotensin II-induced hypertension and chronic renal damage. Hypertension 2012; 59:136–144.

51. Lukic L, Lalic NM, Rajkovic N, *et al.* Hypertension in obese type 2 diabetes patients is associated with increases in insulin resistance and IL-6 cytokine levels: potential targets for an efficient preventive intervention. Int J Environ Res Public Health 2014; 11:3586–3598.

52. Bautista LE, Vera LM, Arenas IA, Gamarra G. Independent association between inflammatory markers (C-reactive protein, interleukin-6, and TNF-alpha) and essential hypertension. J Hum Hypertens 2005; 19:149–154.

53. Nguyen H, Chiasson VL, Chatterjee P, *et al.* Interleukin-17 causes Rho-kinase-mediated endothelial dysfunction and hypertension. Cardiovasc Res 2013; 97:696–704.

54. Madhur MS, Lob HE, McCann LA, *et al.* Interleukin 17 promotes angiotensin II-induced hypertension and vascular dysfunction. Hypertension 2010; 55:500–507.

55. Liu W, Wang X, Feng W, *et al.* Lentivirus mediated IL-17R blockade improves diastolic cardiac function in spontaneously hypertensive rats. Exp Mol Pathol 2011; 91:362–367.

56. Brands MW, Banes-Berceli AK, Inscho EW, *et al.* Interleukin 6 knockout prevents angiotensin II hypertension: role of renal vasoconstriction and janus kinase 2/signal transducer and activator of transcription 3 activation. Hypertension 2010; 56:879–884.

57. Tran LT, MacLeod KM, McNeill JH. Chronic etanercept treatment prevents the development of hypertension in fructose-fed rats. Mol Cell Biochem 2009; 330:219–228.

58. Venegas-Pont M, Manigrasso MB, Grifoni SC, *et al.* Tumor necrosis factor-alpha antagonist etanercept decreases blood pressure and protects the kidney in a mouse model of systemic lupus erythematosus. Hypertension 2010; 56:643–649.

59. Ramiro S, Gaujoux-Viala C, Nam JL, *et al.* Safety of synthetic and biological DMARDs: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis 2014; 73:529–535.

60. ■ Hugh J, Van Voorhees AS, Nijhawan RI, *et al.* From the Medical Board of the National Psoriasis Foundation: the risk of cardiovascular disease in individuals with psoriasis and the potential impact of current therapies. J Am Acad Dermatol 2014; 70:168–177.

This literature overview examined cardiovascular outcomes in patients treated with anti-TNFα therapies. The data suggest reduced cardiovascular events in psoriatic patients treated with anti-TNFα therapeutics.

61. ■ Brown G, Malakouti M, Wang E, *et al.* Anti-IL-17 phase II data for psoriasis: a review. J Dermatolog Treat 2014. [Epub ahead of print]

This recent review provides an early profile of side-effects of IL-17 inhibitors. In particular, the authors discussed possible differences between targeting of IL-17A specifically versus the IL-17R which effectively blocks both IL-17A and IL-17F actions.

62. Paula FS, Alves JD. Nontumor necrosis factor-based biologic therapies for rheumatoid arthritis: present, future, and insights into pathogenesis. Biologics 2014; 8:1–12.

63. Williams SC. Flurry of deal-making surrounds new autoimmunity target. Nat Med 2013; 19:1078.