Therapeutic targeting of inflammation in hypertension: from novel mechanisms to translational perspective

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**Online Supplementary data**

**Methods**

To evaluate evidence regarding the role of inflammation in hypertension we conducted a review of data pertaining to 1) BP outcomes with immunomodulatory medications, selected for inclusion on their ability to illustrate a broad range of pharmacological classes, 2) effects of antihypertensive pharmacological agents on immune and inflammatory parameters, and 3) non-pharmacological approaches targeting inflammation in hypertension. The systematized approach was adopted, as data was largely not adequate to complete meta-analysis according to PRISMA requirements. The population comprised any disease group requiring immunomodulatory medication (the intervention), with comparisons where possible of placebo groups, and normotensive versus hypertensive. Data extracted included design of study including use of randomisation or placebo-control; cohort size, therapeutic agent and dose; duration of follow up with 12 month data chosen if numerous time points available, baseline blood pressure values, change in blood pressure (and any statistical analysis of), and other cardiovascular outcome measures. Ethical approval was not required due to the review nature of the study.

With regard to the human data only, Embase and Pubmed Search Strategies included search terms: blood pressure, hypertens*, inflammatory disease, transplant*, effect, impact, action, tacrolimus, ciclosporin, abatacept, belatacept, rituximab, mycophenolate, basiliximab, infliximab, etanercept, tocilizumab, vascular stiffness, PWV. Furthermore, we also searched ClinicaTrials.Gov for “hypertension” to capture additional studies actively recruiting, or as of yet unpublished. 479 registered trials were screened; 31 in detail, one contributing to the publication. Papers published subsequent to the date of the literature search (03/05/2019) were included if deemed critically relevant to the topic and otherwise met the criteria.

Studies were excluded if duplicates, if based on animal models, participant number was 5 or less, they were review articles (though systematic reviews are referred to if offering additional perspective), were not directly relevant e.g. referred to pulmonary hypertension. Studies of potential value but without reported blood pressure values were contacted to request blood pressure data, though not always successfully.

Adequate number of studies and data were available for meta-analysis of TNF-α inhibitors alone; protocol for assessing inclusion eligibility was as follows:

1) Full-length publication in peer-reviewed journal, or abstract presented at international meeting.

2) Administration of TNF- α inhibitor for a minimum of 6 weeks, for any disease indication.

3) Cross-over, placebo-controlled, and head-to-head comparison studies included.
4) Other immunomodulatory medications not an exclusion if adequately controlled for.

5) Data retrieved included proportion with hypertension or on anti-hypertensive medications; baseline and follow up blood pressure (systolic and diastolic), change in BP and confidence interval as published, or calculated.

6) Minimum number of participants 5; case reports excluded.

On the basis of this protocol, 880 abstracts were reviewed pertaining to TNF-α inhibitors and BP outcomes; 862 excluded on the above grounds; 2 added from search of citations and subsequent publications, and final number included in qualitative synthesis of the paper totaled 20.

Supplementary Table. Blood pressure outcomes of therapeutic agents targeting the immune system.

| Drug class | Reference     | Population | Design (Observational unless specified) / follow-up / comparator | SBP Baseline | SBP Treated | Δ SBP (95% CI, or SD) | P value | Notable and confounding features |
|------------|---------------|------------|------------------------------------------------------------------|--------------|-------------|----------------------|---------|----------------------------------|
| HCQ        | Rho 2009      | N=42       | Current use (cross-sectional) Vs other DMARDs (n=134)             | 136 ± 20     | 127 ± 21    | -8.8                 | 0.01    | 53% of whole cohort (90/169) had HTN, not broken down by drug class. Beta (adjusted for known confounders) -4.59 (-9.99--0.82), P = 0.1 |
| HCQ        | Baker 2018    | N= 7147 (15% F) | Observational (database interrogation) 26 wks Pre-/post-HCQ | 130 ± 17     | Not reported | -1.2                 | Not reported | 77% HTN
                                           Based on proportion with optimal BP, MTX RR 1.09 P<0.0001; Leflunomide RR 0.97 (NS); HCQ RR 1.07 P<0.0001; TNFi RR 1.05 P<0.05.
                                           Multivariable Model evaluating Δ SBP: MTX as reference; Leflunomide β 1.82 (1.2 to 2.5) P<0.001; TNFi β 0.9 (0.3 to 1.5) p=0.003; HCQ β -0.31 (-0.9 to 0.3) NS. |
| HCQ        | Gao 2017      | N=14 (9 F) | FU 52 wks Pre/post-HCQ Pre/post Losartan comparator           | 119 ±12      | 116 ± 9     | -3                   | NS      | All on losartan (standard care)
                                           Neither pre-/post-HCQ nor between-group differences statistically significant. |
| RTX        | Provan 2015   | N=24 (17 F) | Observational;12 wks Pre/post RTX Pre/post ABT comparator      | 128 ± 16     | 109 ± 11    | -1.3 ± 10.1          | 0.53    | RTX vs ABT Δ SBP 0.85 (beta -8.8 (-14.6,-3) |
| Study | RA/Other | Age | Weeks | Pre/Post | BP Change | p-Value | Notes |
|-------|----------|-----|-------|---------|-----------|---------|-------|
| Novikova 2016 | N=55 (55 F) | 50 | 26 wks | Pre/post-RTX | 119 ± 2.4* | 0 | NS | Concurrent DMARDS in 47/55, steroids in 44/55, NSAIDs in 54/55 | * BP in RTX responder subgroup, n= 41 (non-responder group: 112 ± 2.8, to 125 ± 2.4) |
| Mathieu 2012 | N=33 (29F) | 61 | 52 wks | Pre/post-RTX | 130 ± 21 | ‘No change’ | 26/33 concurrent DMARDs | 13/33 concurrent anti-hypertensive |
| Remuzzi 2002 | N=8 (4 F) | 52 | 4 wks | Pre/post-RTX | 131 ± 2 | 136 ± 4 | -5 | NS | BP likely reflects disease treatment, with SBP back to baseline by week 20 (130 ± 5 mmHg) |
| Andreassen 2019 | N=43 (12 F) | 51 | Randomised; 52 wks | Pre/post-CIC: EVR comparator (n=40): | 136 ± 16* | 135 ± 10 | -1 (-17,15) | NS | *Baseline BP recorded at 2 weeks may reduce confounding from early physiological changes. Used ABPM. EVR arm also on CIC until week 7 to 11. Concurrent MMF and steroids. Δ SBP 8 mmHg more in the EVR arm vs CIC (95%CI 0, 15), P = 0.05. Anti-hypertensive drug use: CIC 80% to 90%; EVR 78% to 69%, P= 0.14 |
| Fijter 2017 | N=356 (104 F; 125 CIC and 231 TAC) | 47 | Randomised; 2yrs vs EVR (n=359) comparator | 132 | 132 | 0 | NS | HTN as cause of ESRD equal both groups. HTN as adverse event during FU equal both groups. Concomitant mycophenolic acid and steroids. |
| Chamienia 2014 | N=14 (5 F); age 41 N=15 (7 F); age 46 | 47 | Randomised; 2yrs Pre/post high-TAC Pre/post low-TAC | 131 ± 15 | 132 ± 12 | -5.6 | NS | HTN as cause of ESRD equal both groups. Difference in TAC levels between groups lost by 24 months. BP reported at multiple time points, with variability by FU period and no consistent difference between groups. |
| Larson 2006 | N=84 (40 F) | 48 | Randomised; 52 wks Pre/post TAC vs SRL (n=81) | 130 ± 12 | 120 ± 14 | 0.3 | NS | Antihypertensive drugs could be commenced, but proportion of patients on drugs fell over the study period |
| Murbraech 2015 | N=27 (9 F) | 58 | Randomised; 3yrs Pre/post CIC Pre/post EVR comparator | 142 ± 15 | 140 ± 14 | -6 | 0.08 | Mixed model for difference between groups from baseline to 3 yrs FU P=0.96 No difference in antihypertensive use (P= 0.97) between groups of time-points. |
| Claes 2012 | N=1645 (33-38% F) | 46 | Randomised; 52 wks Std CIC (n= 390) Low-CIC (n= 399) Low-TAC (n= 401) | 144 | 133 | -11 | Low-CIC vs low-TAC -4 mmHg, P<0.05* | Concomitant MMF and corticosteroids. Daclizumab induction to all patients except Std-CIC group. Antihypertensive drug use: 77%, no between group difference, P=0.61 | * After adjustment for multiple comparisons |
| Study              | ± metabolic syndrome | Low-SRL (n= 399) | 144 | 131 | -13 | Not reported | Not reported | 92/339 HTN; over half taking lipid lowering and/or antihypertensive medication at baseline. Concurrent MMF and steroid as standard. No change baseline to 24wks in number of antihypertensive drugs. |
|--------------------|----------------------|------------------|-----|-----|-----|--------------|--------------|---------------------------------------------------------------|
| N=339 (27 F) Kidney Tx HTN subgroup n=92; age 57 | Multi-centre, single arm 24 wk cross-over from CIC to TAC HTN subgroup: | 109 | -5 (-6, -4) | -8.2 (-11, -6) | | | |

**CNI Rostaing 2012**

- N=89 (56 F) Kidney Tx Age 50
- Randomised. 2 yrs Pre/post CIC Pre/post EVR comparator* (n=96) Pre/post MPS* (n=39)
- ESRD due to HTN in 16.5%. Basiliximab induction; CIC, MPS, prednisolone until randomization at 6 months.
- Mean number of antihypertensives 1.95 (±1.28) to 2.08 (±1.07) P<0.005 *Between groups P=0.37

**CNI Van Dijk 2018**

- N=50 (18 F, age 53) Psoriasis
- Randomised to SEC (N=50), CIC, or MTX (N=50) 52 wks FU Pre/post CIC
- Similar rates of baseline hypertension across groups (28-32%). No between group statistical comparisons made * Bonferroni-adjusted P value

**CNI Makavos 2020**

- N=59 (18 F) Kidney Tx Age 54
- Randomised; 3 yrs CNI withdrawal: MMF withdrawal comparator (n=50): ABPM. >60% on BP medications. Difference between the groups at FU: P=0.004. Decline in BP in CNI withdrawal (slope daytime SBP, -1.6 mm Hg/y, P=0.018) not seen in MMF withdrawal.

**CNI Mourer 2013**

- N=50 (15 F) Liver Tx Age 54
- Randomised; 52 wks CNI reduction: MMF up-titrated, then CNI tapered to trough levels 2-4 ng/mL (TAC) or 25-50 ng/mL (CIC).

**CNI Schrama 2000**

- N=15 (9 F) Kidney Tx Age 47
- Open, prospective, pre-/post-CNI withdrawal 8 wks
- CIC tapered (stopped by 32 wks); MMF and 7.5mg prednisolone continued. ABPM.

**CTLA4 Ursini 2015**

- N=15 (7 F) RA Age 53
- Observational; 24 wks Pre-/post-ABT
- Concomitant DMARDs (all on MTX, 4/15 on HCQ) but no prior biologics. 5/15 on ACEi/ARB.

**CTLA4 Mathieu 2013**

- N=21 (17 F) RA Age 65
- Observational, 26 wks Pre-/post-ABT
- 17/21 on DMARDs ± NSAIDs in TNFi non-responders

**CTLA4**

- N=5 (5 F) 12 wks
- RTX vs ABT Δ SBP 0.85 (beta -8.8 (-14.6,-3)
| Study Year | N | Age | Disease | Comparator | Baseline HTN | Treatment | Notes |
|------------|---|-----|---------|------------|-------------|-----------|-------|
| Provan 2015 | 4 | RA 54 | Pre/post-ABT: | 109 ± 11 | 1.3 ± 10.1 | 0.53 | Concurrent MTX ± steroids/NSAIDs. Prior TNFi use similar across groups. |
| CTLA4 Elmedany 2019 | 22 | RA 48 | Pre/post ABT comparator: | 119 ± 15 | 2.2 | 0.36 | *Between group difference SBP at FU 8.5mmHg P = 0.002 |
| CTLA4 Lasella 2018 | 23 | Lung Tx, CNI 'failure' | Conversion CNI to BELAT; MAP Median 19 wks FU | 98 | -5.4 | 0.38 | Induction therapy: almetuzumab or basiliximab; maintenance: TAC, MMF, and prednisolone, with TAC to BELAT switch as intervention |
| CTLA4 Malvezzi 2019 | 24 | Kidney Tx | Conversion CIC to BELAT | 146 ± 19 | -8.8 | 0.3 | Median time Tx to conversion to BELAT was 3.3 years. |
| CTLA4 Vincenti 2010 | 25 | Kidney Tx | BELAT vs CIC | 139 | -6 | 0.027* |
| CTLA4 Seibert 2014 | 26 | Kidney Tx | Baseline HTN 100% CIC group, vs 87% BELAT group | 137 (IQR 121-147) | -9 | 0.68 | Median 39-43% BELAT groups on ≥3 antihypertensives |
| CTLA4 Durrbach 2010 | 27 | Kidney Tx | 52% CIC arm vs 26-29% BELAT groups on ≥3 antihypertensives, p=0.02 |
| MTX Daien 2013 | 28 | RA 51 | Observational cohort: 26 wks FU Pre/post-DMARD Pre/post-ETN n=28 | 121 ± 13 | -1.9 ± 10.9 | NS | Normotensive |
| MTX Mangoni 2017 | 29 | RA 61 | a) Pre-/post-MTX b) MTX vs no-MTX | 125 ± 3 | -4 | 0.006 | ABPM |

* Adjusted for age, gender, BMI, and disease activity score
| Study          | Patients | Disease | Design | Follow-up | SBP Baseline | SBP Change | p Value | Changes from Baseline | Notes |
|---------------|----------|---------|--------|-----------|--------------|-------------|---------|-----------------------|-------|
| MTX Rho 2009  | N=31     | RA      | Cross-sectional comparison between DMARD classes: No LFN vs LFN (n=31) No MTX vs MTX (n=49) | 26 wks | 133 ± 20     | 137 ± 20   | 4       | 0.28                  | Beta (adjusted for known confounders) 5.7 (-0.32–11.73), P = 0.07 Beta (adjusted for known confounders) -1.35 (-6.67–3.97) P= 0.62. |
| MTX Rozman 2002 | N=17   | RA      | Observational; 26 wk Pre/post LFN | 26 wks | 128 ± 19     | 132 ± 21   | 4.3     | 0.003                 | ABPM ± low dose steroid/NSAID |
| MTX Baker 2018 | N=8065  | RA      | Observational (database); 26 wks Pre/post-MTX Pre/post-LFN | 26 wks | 131 ± 17     | 130 ± 17   | -1.4    | Not reported          | MTX 74% HTN; LFN 75% HTN Based on proportion with optimal BP, MTX RR 1.09 P<0.0001; Lefunomide RR 0.97 (NS); HCQ RR 1.07 P<0.0001; TNFi RR 1.05 P<0.05. Multivariable Model evaluating Δ SBP: MTX as reference; Lefunomide β1.82 (1.2, 2.5) P<0.01; TNFi β0.9 (0.3, 1.5) p=0.003; HCQ β -0.31 (-0.9, 0.3) NS. |
| MTX Gyldenløve 2015 | N=32   | RA      | Observational; 8-10 wks Pre/post-MTX | 8-10 wks | 127 (95-160) | 125 (95-165) | -2      | 0.944                 | 16% hypertension at baseline |
| MTX Makavos 2020 | N=50    | Psoriasis | Randomised to SEC (n=50), CIC (n=50), or MTX 52 wks FU Pre/post-MTX: | 52 wks | 128 ± 10     | 130 ± 10   | 2       | 0.7*                  | Similar rates of baseline hypertension across groups (28-32%) No between group statistical comparisons made * Bonferroni-adjusted P value |
| MTX Tam 2012 | N=20    | RA      | Randomised; 26 wks Pre/post MTX: Pre/post MTX+IFX: | 26 wks | 130 ± 24     | 127 ± 15   | -3 ± 15 | 0.79*                 | *Comparison between the changes from baseline between the 2 groups |
| mTOR Fijter 2017 | N=359  | Kidney Tx | Randomised; 2yrs vs CNI (n=356) comparator | 2 yrs | 132         | 132       | 0       | NS                    | HTN as cause of ESRD equal both groups. HTN as adverse event during FU equal both groups. Concomitant mycophenolic acid and steroids. |
| mTOR Andreassen 2019 | N=40   | Cardiac Tx | Randomised; 52 wks Pre/post-EVR: Pre/post-CNI (n=43): | 52 wks | 140 ± 14*    | 132 ± 12   | -8 (-23, 7) | 0.05                  | *Baseline ABPM recorded at 2 weeks. EVR arm also on CIC until wk 7 to 11. All on MMF and steroids. EVR arm Δ SBP 8 mmHg than CIC (95%CI 0, 15), P = 0.05. Antihypertensive drugs: CIC 80% to 90%; EVR 78% to 69%, NS |
| mTOR Gonwa 2003 | N=185  | Kidney Tx | Randomised; multicentre; 26 wks MMF vs SRL | 26 wks | 130 ± 19     | 134 ± 18   | 4       | 0.08                  | Baseline HTN SRL 28.6%, MMF 30.7%. Both groups with concomitant TAC |
| Study | N | Age | Randomised | MMF vs SRL | Pre/post- SRL vs TAC | 137 ± 15 | 135 ± 22 | 130 ± 20 | 135 ± 22 | -2 | 5 | 0.56 | Antihypertensive drugs could be commenced, but proportion of patients on drugs fell over the study period |
|-------|---|-----|------------|------------|---------------------|---------|---------|---------|---------|-----|---|-----|-------------------------------------------------|
| Larson 2006 | 81 (36 F) | 50 | 52 wks Kidney Tx | 142 ± 15 | 136 ± 13 | -6 | -6 | 0.08 | Mixed model: no difference between groups (P=0.96) No difference in antihypertensive use (P= 0.97) between groups. |
| Larson 2015 | 17 (10 F) | 61 | 3 yrs Kidney Tx | 146 ± 20 | 143 ± 22 | -3* | NS | 0.08 | ESRD due to HTN in 16.5%. Basiliximab induction; CIC, MPS and steroid until randomized at 6 mo. *Between group difference P=0.37 |
| Gonwa 2003 | 176 (53 F) | 48 | 26 wks Kidney Tx | 134 ± 18 | 143 ± 17 | 3* | NS | 0.08 | Both groups with TAC. HTN as cause of ESRD in 31% MMF arm vs 29% SRL. |
| Herrera 2006 | 8 (5 F) | 50-65 | Observational. 12 wks FU | 152 ± 6.6 | 137 ± 5 | -15.7 | <0.001 | 4/8 on MTX, discontinued 2 wks previously. 4/8 on anti-hypertensives at baseline. BP reverted after MMF stopped. |
| Mourer 2013 | 60 (21 F) | 52 | Randomised. 3 yrs | 128 ± 12 | 129 ± 10 | -6.6 | NS | 0.004 | ABPM. >60% on BP medications. Difference between the groups at FU: P=0.004. Decline in BP in CNI withdrawal (slope daytime SBP, -1.6 mm Hg/y, P=0.018) not seen in MMF withdrawal. |
| Maes 2003 | 21 (5 F) | 39 | Randomised. 3 yrs | 122 ± 4 | 125 ± 3 | 3 | * | 0.72 | 6/21 on anti-hypertensives already. All started on ACEi as standard. Enalapril dose twice as high in the MMF arm vs placebo (19 vs 11mg) P <0.05. *Linear mixed model treatment effect 0.12; P= 0.72. |
| Tang 2010 | 20 (14 F) | 42 | Randomised. 6 yrs | 120 | 121 | 1 | NS | NS | All on ACEi/ARB as standard. 1.4 anti-hypertensives MMF arm, vs 1.7 control arm. |
| Liu 2014 | 42 (18 F) | 40 | Randomised; 1.5 yrs | 141 | 127 | -14 | Not reported | All on ACEi/ARB as standard. Control group: CIC and prednisolone, n=42 * Between group difference P=0.336 |
| Frisch 2005 | 17 | 40 | Randomised; 2 yrs | 136 | 129 | -7 | Not reported | All on ACEi/ARB ± other antihypertensives to target <130, and higher baseline BP in MMF arm - reduction likely just reflects study protocol to achieve target BP |
| Study                                      | Design                                                                 | Age (years) | Pre/post placebo: (n=15) | 131 ± 11 | 128 ± 6 | 3.6 | 0.002 | Notes                                                                 |
|-------------------------------------------|------------------------------------------------------------------------|-------------|--------------------------|----------|---------|-----|-------|------------------------------------------------------------------------|
| MMF Pascual 2006 39                      | Randomised, multicentre. 3yrs FU MMF w/d vs control arm n=237          | 39          |                          | 136      | 140     |     |       | Single office BP reading.                                              |
|                                           |                                                                        | N=246 Kidney Tx |                          |          |         |     |       | Antihypertensive use at FU: control arm (CNI/MMF/steroid) 66.2%; MMF withdrawal arm 74.4%; P 0.008. Mean number antihypertensives: 1.8 vs 2.0 respectively. |
|                                           |                                                                        | N=58 (12 F) Liver Tx |                          |          |         |     |       | Both arms with concomitant TAC.                                         |
| MMF Cuervas-Mons 2015 40                  | 52 wks Pre/post-MMF: vs pre-/post steroid: (n=59)                      | 56          |                          | 129 ± 25 | 129 ± 22 |   0.6 | 0.88  | Baseline HTN 17% vs 31%. New onset HTN 30.6% (steroid) vs 42.5% (MMF). |
|                                           |                                                                        |              |                          | 124 ± 17 | 132 ± 18 |   7.9 | <0.01 | Antihypertensive use not reported.                                     |
| Interleukin antagonist Thaci 2016 41      | Randomised. 52 wks Pre/post SEC: vs ETN n=303:                         | 312 300mg    |                          | 126.7    | 126.1   | -0.6 | NS    | Demographics and baseline characteristics comparable across groups     |
|                                           |                                                                        | N=315 150mg  |                          | 128.1    | 127.4   | -0.7 |       |                                                                        |
| Interleukin antagonist Makavos 2020 16   | Randomised to SEC or CIC (N=50), or MTX (N=50) 52 wks FU Pre/post SEC | 50 (20 F, age 51) Psoriasis |                          | 130 ± 10 | 124 ± 8 | -6    | 0.3* | Similar rates of baseline hypertension across groups (28-32%)          |
| Interleukin antagonist CANTOS Rothman 2020 | Canakinumab Randomised vs placebo 52 wks                                 | MI with hsCRP >2mg/L Age 59-64* |                          | 130      | Not reported |     | >0.2 | No between group statistical comparisons made                           |
|                                           |                                                                        | N=9549 (25-27% F*) |                          |          |         |     |       | * Bonferroni-adjusted P value                                          |
| Interleukin antagonist Provan 2015 4      | 12 wks Pre/post TCZ Pre/post- ABT (n=5)                                 | 6 F RA Age 52 |                          | 133 ± 22 | 109 ± 11 | -11.5 ± 18.6 | 0.15 | RTX vs ABT Δ SBP 0.85 (beta -8.8 (-14.6,-3)                            |
| Interleukin antagonist Elmedany 2019 22   | Randomised; 24 wks Pre/post-ABT* Pre/post-TCZ*                          | 58 F RA Age 51 |                          | 119 ± 15 | 116 ± 16 | 121 ± 14 | 129 ± 17 | Concurrent MTX ± steroids/NSAIDs. Prior TNFi use similar across groups. |
|                                           |                                                                        |              |                          | 2.2      | 13.7    | 2.2  | 0.36  | *Between group difference SBP at FU 8.5mmHg P = 0.002                 |
|                                           |                                                                        |              |                          | 0.4      |          |     |       |                                                                        |

Studies of immunomodulatory medications in humans reporting SBP outcomes; grouped by mechanism of action. Age: reported average age; FU: follow up; wks: weeks; HCQ: hydroxychloroquine; RTX: rituximab; TCZ: tocilizumab; Tx: Transplant; mTOR: mammalian target of rapamycin; EVR: everolimus; SRL: sirolimus; RR: relative risk; ARR: absolute risk reduction; MTX: methotrexate; LFN: leflunomide; MPS: mycophenolate sodium; BELAT: Belatacept; SEC: Secukinumab. Design – ‘Pre/post’: average SBP before and following introduction of the drug; ‘drug comparator’: BP values before and after introduction of alternate drug are provided for comparison; ‘Vs drug’ = difference between groups reported. SBP: mean ± SD.
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