Colchicine for patients with diabetic nephropathy?

A Randomized control study

Diabetic nephropathy

- The leading cause today for ESRF in the western world.
- Multifactorial intervention may slow the rate of albuminuria and renal injury:
  - Glycemic control
  - HTN control
  - ACE-I/ARBs
- Other treatments failed currently:
  - Aliskerin, a direct rennin inhibitor
  - bardoxolone methyl
  - Dietary protein restriction
  - Pentoxifyline
  - Endothelin receptor antagonists
  - Protein kinase C inhibitors

Inflammation in DN

- Recently researchers suspect that inflammatory pathways play central roles in the progression of DN

- There is evidence that DM has an auto-inflammatory component with Nlrp3 inflammasome and IL-1 β activation (part of the innate immune system)

Innate mediated Inflammation in DN

- Glomeruli expression of adhesion molecules, cytokines (IL-1, IL-6, IL-18 , TNF) and chemokines
- Monocyte/macrophage infiltration
- Transcription factors, mainly, NF-κB,
- IL-1β over-expressed in beta-cells of patients with DM and promote their apoptosis.
- Several RCT's using monoclonal antibodies directed against IL-1β (Gevokizumab, LY2189102), showed benefit in improved glycemic control and reduced inflammation in DM2 patients.

- These studies and other suggest that activation of the innate immune system is a major contributor to the chronic inflammatory state in DM2.

Colchicine

- Relatively safe anti-inflammatory drug
- Used to treat and reverse albuminuria in FMF nephropathy, an auto-inflammatory disease
- The pathogenesis of FMF and auto-inflammatory diseases is related to activation of the inflammasome *via* Nf-KappaB, and Interleukin -1 pathways

FMF and DN

- Colchicine can reverse proteinuria in FMF patients with amyloidosis, if given before uremia developed
- Anti Il-β monoclonal antibodies which are clearly effective in treatment of FMF have shown some promising results in recent RCT's in DM2 patients. mg/day).

Colchicine reduces proteinuria in rats with experimental DM

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Colchicine attenuates inflammatory cell infiltration and extracellular matrix accumulation in diabetic nephropathy

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- This effect was attributed to its anti-inflammatory effect:
  - Attenuated mesangial inflammatory cell infiltration, possibly by inhibiting:
    - Monocyte chemotactic protein-1(MCP-1)
    - Intercellular adhesion molecule-1 (ICAM-1)

Colchicine and cyclosporine-nephrotoxicity

- Colchicine prevents renal injury in cyclosporine-nephrotoxicity model in rats and anti GBM model in rabbits.

Disel, U., et al., Effect of colchicine on cyclosporine nephrotoxicity, reduction of TGF-beta overexpression, apoptosis, and oxidative damage: an experimental animal study. Transplant Proc, 2004. 36(5): p. 1372-6.

Li, C., et al., Colchicine decreases apoptotic cell death in chronic cyclosporine nephrotoxicity. J Lab Clin Med, 2002. 139(6): p. 364-71.

Aim and hypothesis

Aims of the Study:

A randomized controlled pilot study to test the efficacy and safety of colchicine treatment for DN.

Working hypothesis

DN patients treated with colchicine will have a significant reduction in the progression of proteinuria compared to placebo, with minimal side effects

Methods

- 40 DN patients will be randomized to receive oral colchicine or placebo at a ratio of 1:1. (supplied by RAFA)
- Colchicine treatment will be initiated at 1mg per day, and increased to 2 mg if tolerated
- Both groups will be treated for 18 months.
- 24 hr. Protein will be assessed at:
  - 3 mo. before initiation
  - At baseline
  - Every 3 mo. during the study period
  - A year after end of treatment
- At Screening and at end of study thorough assessments

Thorough assessment at screening and end

- 24 hr urine collection for protein.
- Urine protein-to-creatinine ratio (UPCR) in a spot first- or second-morning urine sample after avoiding exercise
- Blood creatinine
- Complete blood count
- Creatinine phosphokinase (CPK)
- Liver function tests
- Fasting Glucose Test and HbA1c
- DM treatment monitoring and comprehensive clinical follow-up, other treatments
- Blood pressure
- Total cholesterol, LDL-C, HDL-C, TG

Inclusion criteria:

- Patients with DM, age>18 years old, able to sign an informed consent.
- 24 hr. proteinuria >0.5 gr.
- Hemoglobin A1c in the range of 6-9%, stable for last year (0.5±)
- Blood creatinine lower than 2 mg/dL.
- Blood pressure lower than 140/90 mmHg on stable anti-hypertensive treatment for at least 3 months.
- Treated with ACE or ARB, unless contraindicated

Exclusion criteria:

- Malignancy or significant heart, lung or liver disease.
- Any GI disease, IBD, malnutrition (BMI under 18)
- Psychiatric disease
- Any muscle disease, history of rhabdomyelitis, myopathy or myositis.
- Any disease causing renal injury/proteinuria apart from DM
- Any inflammatory or autoimmune disease
- Any infection during the last month.

Outcome measures:

- Stabilization or decrease of proteinuria of the treatment group compared to placebo and to initial tests
- Stabilization or decrease of fasting glucose or HbA1C

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