Immunological Aspect of Ozone in Rheumatic Diseases

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Rheumatoid arthritis is an autoimmune disease.

Rheumatoid arthritis is associated with immunological and inflammatory mechanisms. The initial, not yet well defined immunological mechanisms lead to inflammatory reactions which alter between acute and chronic stages.
Exogenous mechanisms \[\rightarrow\] Immuno-inflammatory response \[\rightarrow\] Endogenous mechanisms

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The question of balance

Natural predisposition to disease \[\rightarrow\] Pro-inflammatory cytokines

Natural host defense \[\rightarrow\] Anti-inflammatory cytokines

Symptoms, tissue lesions
Cytokine disequilibrium

PROINFLAMMATORY
- TNF
- IL-1
- IL-6
- IL-8
- IFN-γ
- LTα

ANTI-INFLAMMATORY
- IL-4
- IL-10
- TGFβ
- sTNFR
- sIL-1R
- IL-1Ra

Physical manifestations

- Joints usually involved symmetrically, with wrists, MCP joints, and PIP joints most commonly affected\(^1\)

- Articular manifestations include tenosynovitis, which diminishes strength and flexibility\(^1,2\)

- Extra-articular manifestations most prevalent when RF is positive; up to 50% of patients demonstrate nodules\(^1,2\)

RA: IMPACT, PATHOGENESIS, AND TREATMENT

The inflammatory cascade

- Activation of T cells triggers a series of intercellular reactions\(^1\)

- Lymphocytes and macrophages release proinflammatory cytokines\(^{1,2}\)

- Cytokines induce synovial proliferation and release of destructive enzymes\(^{1,2}\)

The role of cytokines

- Serve as natural mediators of cell function\(^1\)
- Induce production of other cytokines\(^2\)
- Reduce inflammation by binding to cell-surface receptors or preventing cell activation\(^3\)

Importance of targeting TNF

- The binding of TNF to cell-surface receptors triggers multiple destructive events\(^1\)

- TNF induces production of other proinflammatory cytokines, including IL-1\(^1\)

- Thus, targeting TNF may inhibit the destructive activity of both TNF and other destructive cytokines\(^2,3\)

The central role of TNF

- **Drives events in the inflammatory cascade**¹,²
- **Triggers production of other cytokines, including IL-1**¹,²

![Diagram showing the central role of TNF in inflammation](image)

References:

Adapted from Feldmann et al, 1996.¹
Destructive effects of TNF

1. TNF
   - osteoclasts: bone resorption → bone erosion
   - synoviocytes: joint inflammation → pain/joint swelling
   - chondrocytes: cartilage degradation → joint space narrowing
IL-1 Plays a Pivotal Role in Many Mechanisms of the RA Disease Process

- Synovial inflammation
- Bone destruction
- Impairment of tissue repair process
- Pannus formation
- Production of prostaglandins and inflammatory mediators
- Cartilage degradation

RA is Characterised by Synovitis and Joint Destruction

**NORMAL**
- Synovial membrane
- Cartilage
- Capsule

**RA**
- Inflamed synovial membrane
- Pannus
- Synovial fluid
- Cartilage thinning
- Major cell types:
  - T lymphocytes
  - Macrophages
- Minor cell types:
  - Fibroblasts
  - Plasma cells
  - Endothelium
  - Dendritic cells
- Major cell type:
  - Neutrophils

IL-1 Plays a Pivotal Role in the Inflammatory and Destructive Processes of RA

IL-1

- Activates monocytes/macrophages
- Induces fibroblast proliferation
- Activates chondrocytes
- Activates osteoclasts

Inflammation
Synovial pannus formation
Cartilage breakdown
Bone resorption

Role of IL-1 in Joint Destruction

- IL-1 has a higher potency for inducing joint destruction than TNF$^1$
- In TNF-transgenic mice, arthritis can be completely inhibited by blocking IL-1 signalling$^2$
- TNF-independent IL-1 production has been shown in models$^3$
- No erosive arthritis is observed in IL-1β-deficient mice$^4$
- Spontaneous, destructive arthritis is observed in IL-1Ra-deficient mice$^5$

3. van den Berg W. *Ann Rheum Dis.* 2000;59(suppl 1):i81-i84;
IL-1 Plays a Central Role in Cartilage Destruction

- Proteoglycan synthesis (aggrecanase)
- Collagen damage (↑proMMP-13, ↓type II collagen)
- Immune complex deposits
- Cartilage surface erosion (pannus, PMN)
- Chondrocyte death (NO, iNOS)

iNOS = inducible nitric oxide synthase; MMP = matrix metalloprotease; NO = nitric oxide; PMN = polymorphonuclear cell

IL-1 Regulates Osteoclast Differentiation and Activity

IL-1 regulates osteoclast differentiation and activity. IL-1 induces osteoclast progenitor to differentiate into osteoclasts. IL-1 also induces osteoblast apoptosis.

OPGL = osteoprotegerin ligand

The effect of ozone of the immune system

1. The effect of the immune competent cells of the lymphocytes

2. The induction of the cytokinin through the effect of the lymphocytes

3. Regulation of the immune system
Ozone-activated immunocompetent cells respond by production and release of cell-specific cytokins in a physiological manner. Cytokins represent the dialogue-molecules among the immunocompetent cells, such as Interferons, Interleukins, Growthfactors.
Cytokine-Induction (in %)

In dependence on ozone concentration
The evolving RA treatment paradigm

**CURRENT APPROACH**

**EARLY TREATMENT**
- Traditional DMARDs

**IF POOR RESPONSE**
- Add additional DMARDs
- Add biologic agent

**EVOLVING PARADIGM**

**EARLY TREATMENT**
- Aggressive DMARD therapy
- Biologic agent
- Monotherapy or Combination

**IF POOR RESPONSE**
- Combination therapy

**IF DISEASE CONTROLLED**
- Discontinuation/reduction of DMARDs
Study identification and inclusion criteria

Groups of patients with Rheumatoid Arthritis
each group n = 25 patients

1. Group:
   - NSADs Diclofenac 100 – 150 mg

2. Group:
   - Ozone 3 x weekly

3. Group:
   - Ozone + Methotrexat 7,5 – 15 mg

4. Group:
   - Ozone + Enbrel 50 mg weekly + MTX 7,5 – 15 mg
Serum CRP concentration (mg/l) over time

- **Mean score (+/-se)**

- **Ozone**
- **MTX**
- **MTX+Ozone**

**Study Day**
- 0
- 30
- 60
- 90
- 120
- 150
- 180
Patient assessment of disease activity over time (group 1 and 2)

Study Day

- Pain At Rest
- Tenderness
- Pain active Mot.
- Joint Swelling
- Joint Effusion

Graph showing disease activity over time with different symptoms assessed on various study days.
Patient assessment of disease activity over time (group 3 and 4)
The effect of different groups of the cytokines
Improvement baseline, 180 days: MTX-Enbrel-Ozone

Days:

- Pain at rest
- Tenderness
- Pain active mot.
- Joint swelling
- Joint effusion

Severity:

- 3.5
- 3
- 2.5
- 2
- 1.5
- 1
- 0.5
- 0
Improvement baseline, 180 days: (without Ozone)
Summary

1. Ozone is more effective in combined form than single form in the treatment of RA

2. Ozone provided efficacy comparable to combination of MTX

3. Rapid significant decrease in CRP and ESR in combined form (MTX and Ozone) than in single form

4. The incidence of clinically significant treatment in relation to laboratory abnormalities was similar among treatment groups with NSADs

5. The ability of ozone to reduce level of acute phase Proteins, and Enbrel in the blood was significant greater in combined form than in single form

6. The ozone effect of the cytokines could be due to either inhibition of the production of cytokines or inhibition of response to cytokines

7. Ozone in clinically and biochemical superior in combined form than single form in treatment of RA
The Applications of Ozone Therapy in Pain Management, Rheumatic and Orthopaedic Diseases
Vielen Dank für Ihre Aufmerksamkeit

Thank you for your kind attention