ERYTHROPOIETIN IN ANIMAL MODELS OF INFLAMMATION

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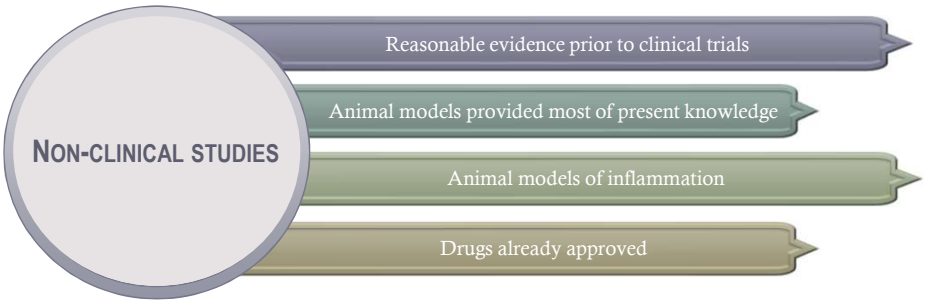
Lisbon, May 2021

INTRODUCTION



Park et al., 2019
Vandamme et al., 2014
Talevi et al., 2020

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Erythropoietin (EPO) is a potent stimulator of erythroid progenitor cells.

GLYCOPROTEIN HORMONE

- Mostly produced in the renal cortex
- Homodimeric and heterodimeric receptor

MAIN REGULATOR OF ERYTHROPOIESIS

- Stimulates production and differentiation of red blood cells in bone marrow

ERYTHROPOIETIC AND NONERYTHROPOIETIC EFFECTS

- Induce erythropoiesis, angiogenesis, tissue regeneration and decreases apoptosis

Chateauvieux et al., 2011
Jelkmann et al., 2011
Vogel et al., 2011

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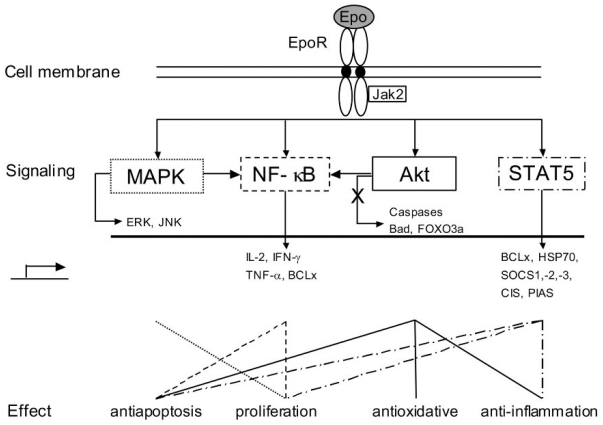
Furthermore, **EPO inhibits NF-kB activation** and proinflammatory gene expression in the lamina propria



Cuzzocrea et al., 2004
Nairz et al., 2011

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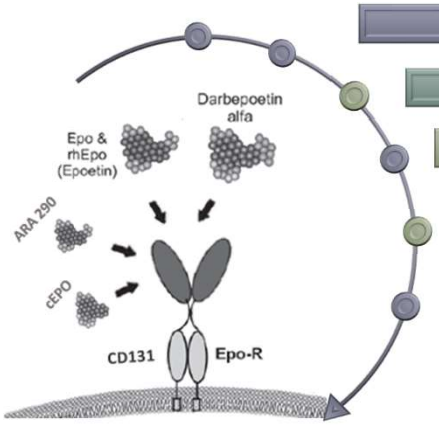
EPO ANALOGUES



- Same biological activity of endogenous EPO
- Acting on the same receptor
- Recombinant Human Erythropoietin
- Same adverse effects of endogenous EPO
- Non-erythropoietic analogues
- Non-erythropoietic effects

Jelkmann et al., 2011
Reichel et al., 2015
Chateauvieux et al., 2011
Jelkmann et al., 2013

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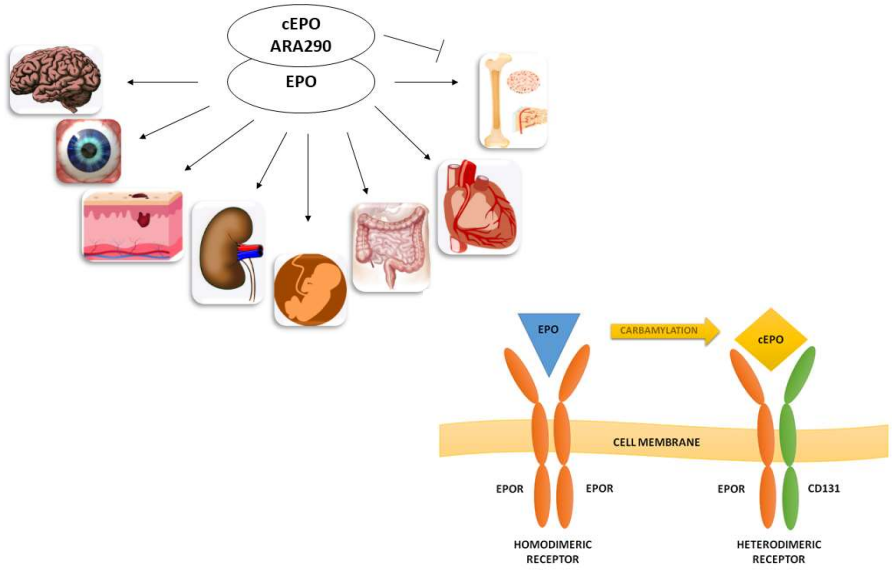

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AIM

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Evaluate the potential anti-inflammatory effect of erythropoietin in non-clinical studies in vivo of rodents

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METHODOLOGY

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Database Platform

MEDLINE via PubMed

Keywords

- Erythropoietin
- Inflammation
- Disease models, animal

PRISMA METHODOLOGY

Inclusion Criteria

1) Only original articles
2) Studies where EPO was administered
3) Studies where EPO was studied and/or evaluated
4) Non-clinical studies in vivo of rodents
5) Articles published in English

Data Extraction

Table of results was created using:

- Erythropoietin-Related parameters
- Animal-Related parameters
- Biomarkers assessed

Rother et al., 2007
Siddaway et al., 2018

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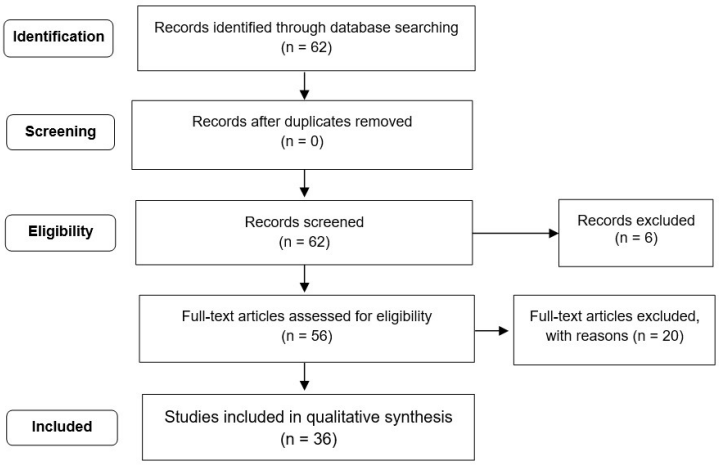

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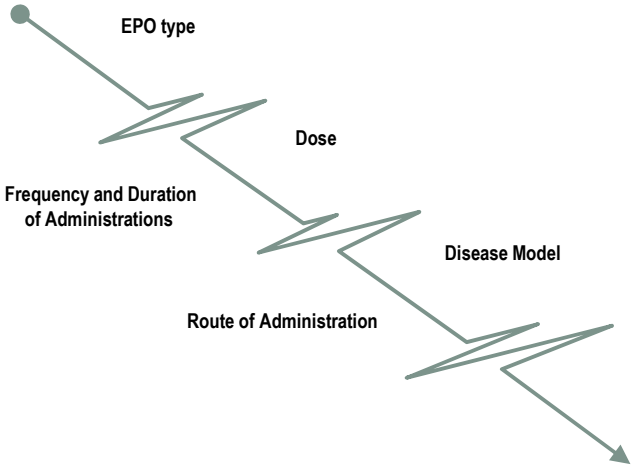
ERYTHROPOETIN-RELATED PARAMETERS



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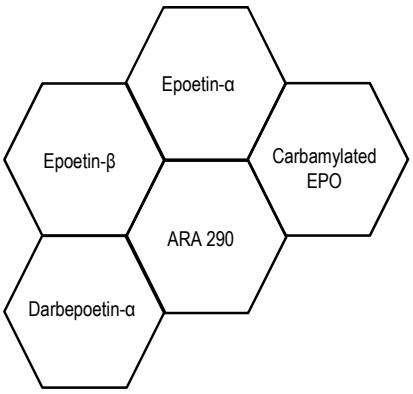
ERYTHROPOIETIN TYPE

- Most articles used only the term rHuEPO (n=22)



Difficult to assume which is the most used and why

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FREQUENCY AND DURATION

- Most studies used a single dose of EPO (n=15), others used it daily (n=10)
- The duration of treatment varied from 3 days to 3 months

Both single doses and multiple doses demonstrated anti-inflammatory effects

Commin et al., 2012

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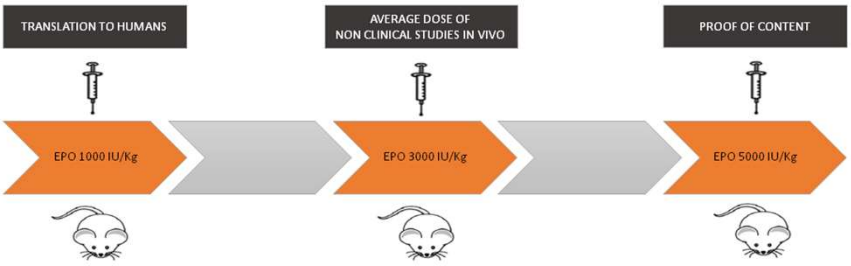
DOSE OF ERYTHROPOIETIN



- Most commonly used doses were 1000 (n=8), 3000 (n=6) and 5000 (n=15) IU/Kg

The average of single and multiple doses were 3000 IU/Kg

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ROUTE OF ADMINISTRATION

- Intraperitoneal route was the most used (n=19)
- Others were also identified as the subcutaneous (n=7) and intravenous (n=4) route

Repeated daily intraperitoneal dosing for up to one month is well-tolerated in rodents

Intraperitoneal administration results in a faster absorption and can be used to administer large volumes

Commin et al., 2012

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DISEASE MODELS

- Most commonly used were sepsis (n=5), traumatic brain injury (n=4) and autoimmune neuritis (n=3)

These disease models triggers an innate inflammatory response

INFLAMMATORY BOWEL DISEASE

Mateus et al., 2016

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ANIMAL-RELATED PARAMETERS

ANIMALS

Rats (n=22)
Mice (n=15)

→ Advantage of ease of maintenance, gene homology and easy handling

STRAIN

Sprague-Dawley (n=10)
C57BL/6 (n=7)

→ Commonly used in many research with docile nature

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ANIMAL-RELATED PARAMETERS

AGE

Rats 3-16 weeks old
Mice 5-16 weeks old

GENDER

Males (n=20)
Females (n=6)

→ Female gender produce a high number of hormones

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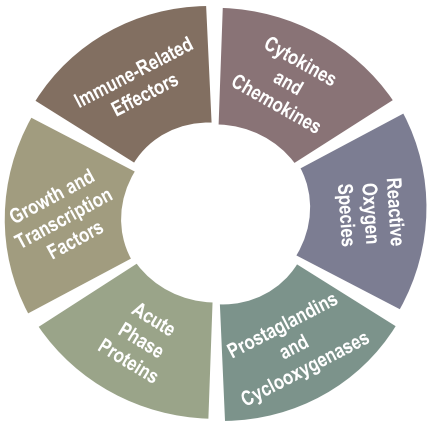
BIOMARKERS ASSESSED



- Main biomarkers measured were TNF-α (n=16) and IL-1β (n=14)

EPO decreased inflammatory response

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CONCLUSIONS

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EPO

- Recognized as a multifunctional anti-inflammatory cytokine
- Potential anti-inflammatory effect

PARAMETERS

- Epoetin-β
- Dose between 3000-5000 IU/Kg
- Rats and mice
- TNF-α and IL-1β biomarkers

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FUTURE PERSPECTIVES

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TREAT INFLAMMATORY-BASED DISEASES

IMPROVE PATIENT'S QUALITY OF LIFE

ENLIGHTENMENT OF ALL PATHWAYS

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TNBS-INDUCED COLITIS

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ANIMALS

Male CD-1 mice, 30-40g in weight and 6-10 weeks of age, were housed in standard polypropylene cages with *ad libitum* access to food and water in the Faculty of Pharmacy Central Animal Facility in the University of Lisbon.

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TNBS-INDUCED COLITIS

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TNBS-INDUCED COLITIS

According to Morris (1989):

- ✓ Mice were left unfed during 24h
- ✓ Mice were anesthetized with Ketamine + Xilazine IP
- ✓ 100µl of TNBS (2,5% TNBS in 50% ethanol) was administered through a catheter inserted into the rectum
- ✓ Mice were kept for 1 min in a Tredelenburg position to avoid reflux
- ✓ EPO 500 – 1000 mg/Kg were daily administrated IP

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TNBS-INDUCED COLITIS

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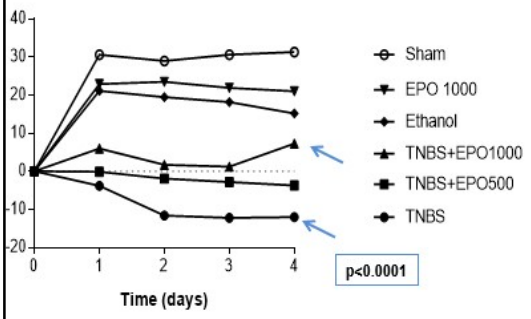
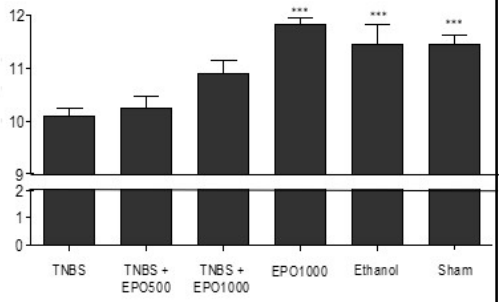
CLINICAL SIGNS

CHANGE OF BODY WEIGHT (%)



COLON LENGTH (cm)



Mateus et al., 2016

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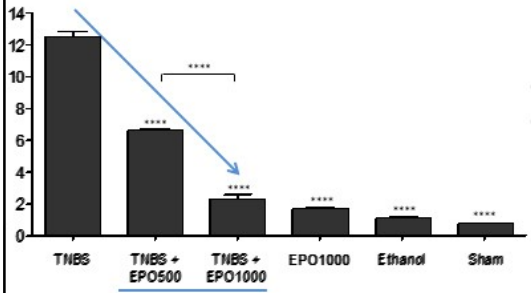
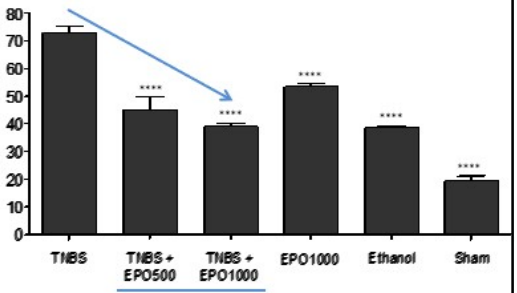
BIOCHEMICAL MARKERS

FAECAL HAEMOGLOBIN (µmol Hg/g feces)



EPO decreased the intestinal bleeding

ALP (UI/L)



EPO seems to decrease the colonic damage

Mateus et al., 2016

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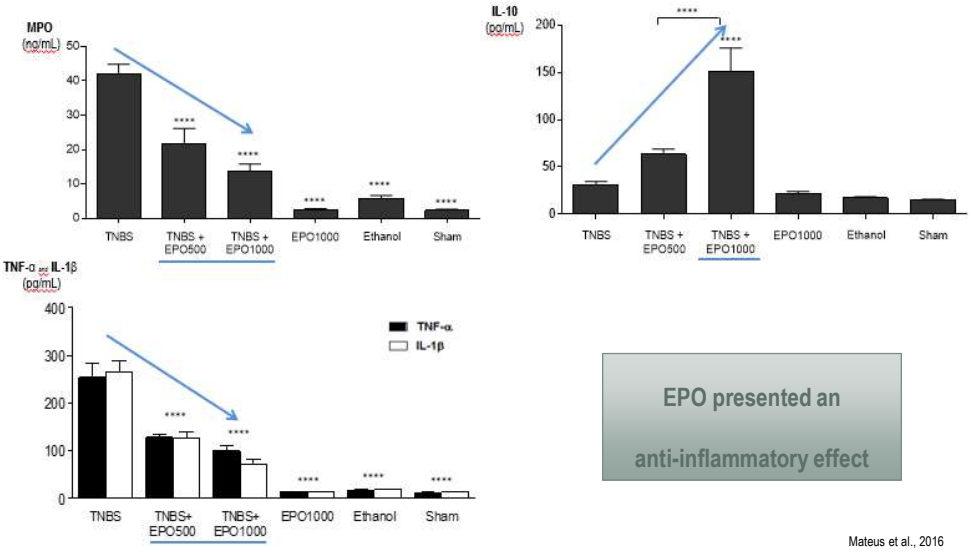
BIOCHEMICAL MARKERS



EPO presented an anti-inflammatory effect

Mateus et al., 2016

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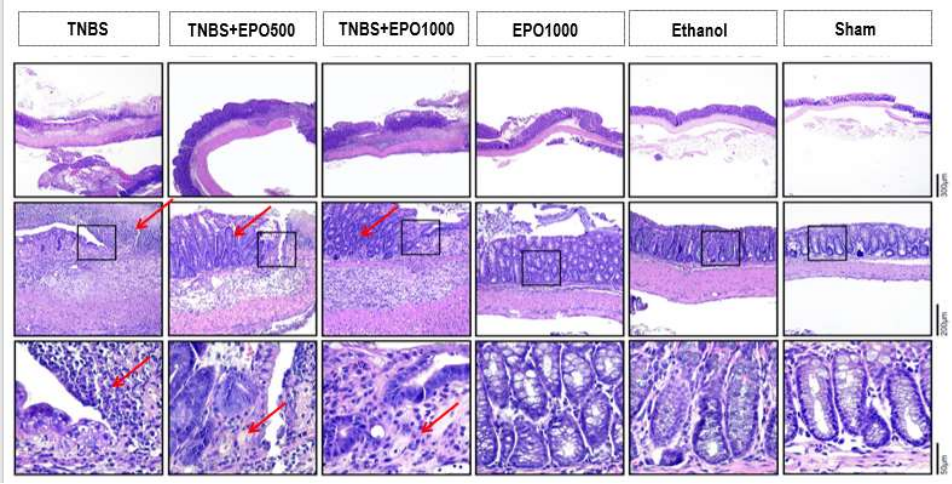
HISTOLOGY



Mateus et al., 2016

Final Conclusions

EPO significantly inhibit the acute inflammatory response in the experimental colitis

This study may possibly contribute to the enrichment of the therapeutic opportunities of IBD

Acknowledgment

Vanessa Mateus, PhD

Rui Pinto, PhD

Inês Silva, PhD student

Rita Modesto, PhD student

Carolina Alipio, Master student

João Solas, Master student

João Estarreja, Bachelor student

Grant: IPL/2020/cEPO_ESTeSL

H&TRC authors gratefully acknowledge the FCT/MCTES national support through the UIDB/05608/2020 and UIDP/05608/2020.

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