Novel anti-inflammatory compounds for ulcerative colitis and rheumatoid arthritis therapy

JANSA, P.¹, HOLÝ, A.¹, ZÍDEK, Z.², JANEBA, Z.¹, KOLMAN, V.¹

¹Institute of Organic Chemistry and Biochemistry AS CR v.v.i.
²Institute of Experimental Medicine AS CR v.v.i.
Inflammatory bowel diseases (IBD)
chronic, relapsing, and remitting inflammatory diseases

Ulcerative colitis UC

Crohn’s disease CD

CLINICAL
Rectal bleeding
Diarrhea
Fever
Fatigue
Weight loss
Abdominal pain

HISTOLOGICAL
Mucin depletion
Crypt distortion and abscesses
Lymphoplasmycatic infiltration

Prevalence
24.3 per 100,000 in Europe
19.2 per 100,000 in North America

Medical costs
Individual UC patient in the USA: $15,020 (average annual expenditure, 2013)
Rheumatoid arthritis (RA)
chronic, autoimmune disorder resulting in chronic and systemic inflammation of joints

**CLINICAL Articular:**
- Joint pain
- Stiffness
- Swelling
- Bone destruction

**Extra-articular:**
- Eyes (scleritis, episcleritis);
- Pulmonary fibrosis
- Myocardial fibrosis
- Hepatomegaly and Splenomegaly
- Osteoporosis

**Prevalence**
- 500-1500 per 100,000

**Incidence**
- 15♂, 36 ♀ per 100,000

**Medical costs**
- Individual RA patient in the USA: $14,900 (average annual cost, 2010)

May 6, 2014
# Current treatment of IBD and RA

## IBD
- **Traditional therapy**
  - Corticosteroids (prednisone; prednisolone)
  - Aminosalicylates (sulfasalazine; mesalazine)
- **Purine-based**
  - Thiopurines (azathioprine, 6-mercaptopurine)
- **Cyclic molecules**
  - Cyclosporine A
  - Macrolides (tacrolimus)
- **Biologic agents**
  - Anti-TNF- (infliximab; adalimumab; certolizumab; golimumab)

## RA
- **Disease-modifying antirheum. drugs (DMARD)**
  - Glucocorticoids (cortison)
  - Aminosalicylates (sulfasalazine; mesalazine)
  - Methotrexate (priority in RA)
  - Leflunomide (alternative to MTX)
  - Hydroxychloroquine
  - Azathioprine
- **Biologic agents**
  - Anti-TNF- (etanercept; infliximab; adalimumab; certolizumab; …)
  - Anti-IL-1 (anakinra)
  - Anti-IL-6 (tocilizumab)
  - Anti-B-cells (rituximab)
  - Anti-T-cells (abatacept)
Current pharmacotherapy and perspectives

Results of current therapeutic strategies clearly highlight the need to develop new therapies.

- All current therapeutic strategies for treating IBD and RA have only been moderately successful.
- A considerable proportion of patients are still refractory to conventional treatment.
- Both, traditional anti-inflammatory drugs and biologics provide partial clinical benefit. They may be associated with significant side effects and toxicity.
- Broader use of biologics is restricted by unfavorable pharmacoeconomy.
- The development of small-molecule compounds with similar efficacies remains an acute unmet medical need in diseases such as ulcerative colitis and rheumatoid arthrits.

May 6, 2014
Novel promising compounds

Pyrimididine derivatives

derivatives of 2-aminopyrimididine

May 6, 2014
Relevant *in vitro* biological activities

Pyrimidine derivatives are inhibitors of nitric oxide (NO), prostaglandin (PGE$_2$) and cytokine production.

Simultaneous inhibition of NO and PGE$_2$ has a promising potential in the treatment of colitis and arthritis.

(Dong et al., World J. Gastroenterol. 9:1307, 2003; Dudhgaonkar et al., Inflammopharmacology 15:188 2007; Sklyarov et al., J. Physiol. Pharmacol. 62:65, 2011)


May 6, 2014
In vivo model of ulcerative colitis

A number of murine models of colitis have been developed. Among various chemically induced colitis models, the dextran sulfate sodium (DSS)-induced colitis model is widely used because of its simplicity and many similarities with human ulcerative colitis. It allows the evaluation of potential therapeutics.

Evaluation:
- Disease Activity Index
  (bleeding; stool consistency; weight loss)
- Colon length
- Histology

![Graph showing index of effectiveness for different compounds compared to sulfasalazine.](image)

Healthy Moderate colitis
Moderate-severe colitis (grade 2)
**In vivo model of rheumatoid arthritis**

**Rat models** of immune-mediated arthritis are the conventional approach to evaluating efficacy of potential therapeutics. The frequently used is the **rat adjuvant-induced arthritis**. It is widely used because of its simplicity and many similarities with human disease.

**Routine screening:**
- **Volume of paw edema** (of uninjected paw; plethymometer)
- Body weight
- Splenomegaly, hepatomegaly

```
May 6, 2014

Rat models of immune-mediated arthritis are the conventional approach to evaluating efficacy of potential therapeutics. The frequently used is the rat adjuvant-induced arthritis. It is widely used because of its simplicity and many similarities with human disease.

Routine screening:
- **Volume of paw edema** (of uninjected paw; plethymometer)
- Body weight
- Splenomegaly, hepatomegaly
```
Development and IP status

• Development status:
  • ~700 original compounds have been prepared and tested (by now)
  • Proof-of-concept was done using rodent arthritis and colitis models
  • Preliminary toxicity data indicated sufficient therapeutic window
  • *p.o.* application is possible and used in animal models
  • Preliminary results of PK, bioavailability and genotoxicity are favorable
  • Lead optimization is under way

• IP status
  • EP and US patent application with priority date in Feb 2011
  • Further patent filing is expected

• The project is offered for co-development and/or licensing.
“Novel anti-inflammatory compounds for ulcerative colitis and rheumatoid arthritis therapy”

CONTACT

Dr. Jaromir Zahradka
e-mail: zahradka@iocb-tto.cz
tel.: +420 220 612 258

This is a project of Center for Development of Original Drugs with the financial support of Technology Agency of the Czech Republic