Erdosteine: a new therapeutic weapon beyond the PEACE

Summary
Due to its multiple mechanism of actions, Erdosteine can be considered one of the most interesting thiol in the long term treatment of COPD and its exacerbations. New findings confirm the potential of this molecule to exceed the PEACE study results, as expected after the RESTORE study conclusion, and they open an additional space for clinical research to treat patients with resistant infections or comorbidity associated to COPD.

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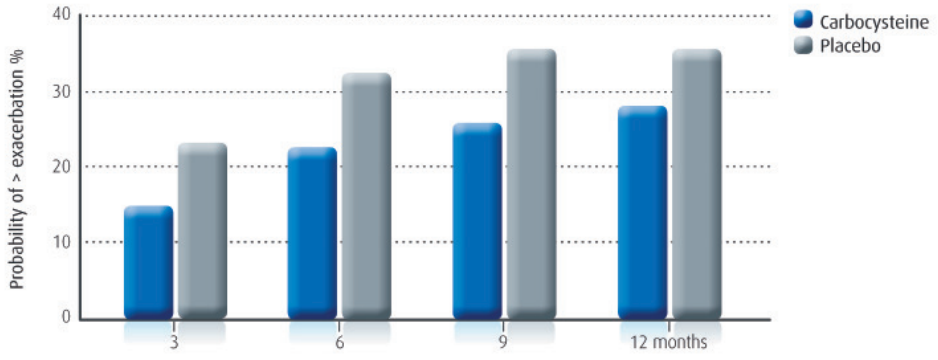
The growth of mortality related to COPD is being well confirmed by the World Health Organization in its most recent studies. The table below shows the evolution of the importance of COPD and its relative importance among the other major causes of mortality. Ageing population and increasing pollution are among the major factors for the COPD evolution (Table 1).
The research of more and more effective therapeutic approaches is therefore an ongoing commitment for the scientific community. It has been following two major paths: the discovering of new drugs and the best administration of already known drugs. For years the major efforts have been focused on the first path but, given the very few new drugs developed in the last years, the importance of the second path is growing.
The pneumologist community had always considered mucolytics necessary for the treatment

Table 1. Change in rank order of deaths for the 10 leading causes worldwide[2].

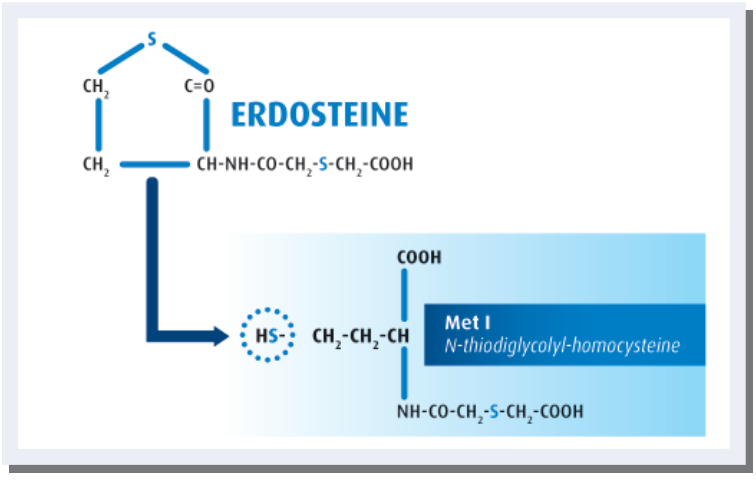
2002	2030
1. Ischaemic heart disease	1. Ischaemic heart disease
2. Cerebrovascular disease	2. Cerebrovascular disease
3. Lower respiratiory infections	3. HIV/AIDS
4. HIV/AIDS	**4. Chronic obstructive pulmonary disease**
5. Chronic obstructive pulmonary disease	5. Lower respiratory infections
6. Perinatal conditions	6. Diabetes mellitus
7. Diarrhoeal disease	7. Trachea, bronchus, lung cancer
8. Tuberculosis	8. Road traffic accidents
9. Trachea, bronchus, lung cancer	9. Tuberculosis
10. Road traffic accidents	10. Perinatal conditions

Figure 1. Probability of exacerbation[1].



of COPD, but the "evidence based medicine" had rightly asked for clear results on life expectancy and quality of life.
In this scenario three large international studies have been planned and developed with similar objectives on the most known thiols with a solid clinical experience on the mucus rheological changes, the N-Acetilcysteine (NAC) (BRONCUS study[1]), the Carboxy-methylcysteine (PEACE study[2]), and the Erdosteine (RESTORE study).
Besides to their clinical experience, the choice of these substances is based on their metabolic role rather than their actions on mucus. Indeed, in order to achieve significant results in the prevention of relapses and reducing the progression of COPD is necessary to rely on effective antioxidant activity, bacteria anti-adhesion and antinflammatory effect. The additional organ protection is a very desirable therapeutical target.
The BRONCUS and the PEACE study have been completed and published[1,2].
The BRONCUS, perhaps because of an inadequate therapeutic dose of NAC has not met the expected results and its conclusions are that the NAC dose of 600 mg a day associated with topical steroid therapy is "ineffective" in slowing the progression of the disease[1].
The PEACE study, gave significant results which allowed Carboxymethylcysteine to be included in the recent update of the GOLD guidelines among the treatment options for COPD[2].
Carbocisteine demonstrated a significant effect on exacerbations and improvement in health-related quality of life (Figure 1).
Despite this promising results, that confirm the role that thiols could play in the treatment of COPD, due to the severity and the related mortality of this pathology we need a step further.
The RESTORE study is still on going in 10 countries, with results expected in 2014. After the PEACE study and waiting for the RESTORE conclusion it is important to reconsider and re-evaluate the old and the new scientific data on Erdosteine.
Erdosteine, N-(carboxymethylthioacetyl) homocysteine thiolactone, is the most recent drug developed in its class.
The molecule of Erdosteine is characterized by the presence of a carboxylic acid group and of two sulphur atoms (Figure 2).
Erdosteine is quickly absorbed

Figure 2. Chemical structure of erdosteine.



after oral administration and rapidly transformed through a first-pass metabolism to a biologically active metabolite – N-thiodiglycolyl-homocysteine (Met I). The chemical structure of Erdosteine results in a compound with a unique multifactorial mechanism: Muco-modulatory, Anti-oxidant activity, Bronchial anti-infammatory and Bacterial anti-adhesion (Figure 2).

Muco-modulatory activity

The muco-modulatory activity of Erdosteine improves the mucus rheological characteristics in terms of viscosity, elasticity and biochemical composition: this is due to the active metabolite I that contains the SH group that cleaves the disulphide bonds in mucin glycoproteins.

The effect of Erdosteine on rheological characteristics of the mucus was evaluated in patients with an exacerbation of chronic obstructive bronchitis[3]. Comparison with each study group, revealed that patients receiving Erdosteine experienced a significant reduction in sputum viscosity at day 3 (-15.8%; $p<0.001$) and at the end of treatment (-39.6%; $p<0.001$) (Figure 3)[3].

A second placebo-controlled study in patients with stable chronic obstructive bronchitis (COB) concluded that Erdosteine provides a statistically significant decrease in the glycoprotein content of mucus (reduction in the macromolecular dry weight of mucus)[4].

Erdosteine improves the mucociliary clearance indirectly through its effect on mucus rheological properties, and by directly acting on ciliary movement.

The effect of Erdosteine on mucociliary transport has been specifically demonstrated in a double blind, placebo-controlled study. Patients were treated for eight days with either placebo or Erdosteine and the mucociliary transport (MCT) assessed using a modified broncho-fiberoscopic technique[5]. Erdosteine induced a statistically significant mean MCT change of +60.4% versus -3.0% reported for placebo-treated patients ($p<0.01$). Moreover, mucus transport progression reached a rate comparable to that of healthy non-smokers in 37.5% of patients in the Erdosteine group[5] (Figure 4).

This active metabolite of Erdosteine - Met I - is formed by the opening of the thiolactone ring with formation of a free thiol (SH) group.

Anti-oxidant activity

The direct free-radical scavenging activity of Erdosteine, Met I, NAC, S-carboxymethylcisteine (S-CMC), and Ambroxol has been examined in vitro by determining their effects on the luminol-dependent chemiluminescence (LDCL)[6,7]. (Figure 5). The LDCL of human neutrophils was statistically significantly inhibited by Met I, from a concentration of 100 μmol/L ($p<0.05$). This value was found to be similar to that obtained by reduced glutathione (GSH) under the same test conditions. All other tested molecules were found to be inactive at this concentration.

Erdosteine confirmed to affect

Figure 3. Mean sputum viscosity before and after treatment with Erdosteine or placebo ($p<0.001$ vs baseline)[3].

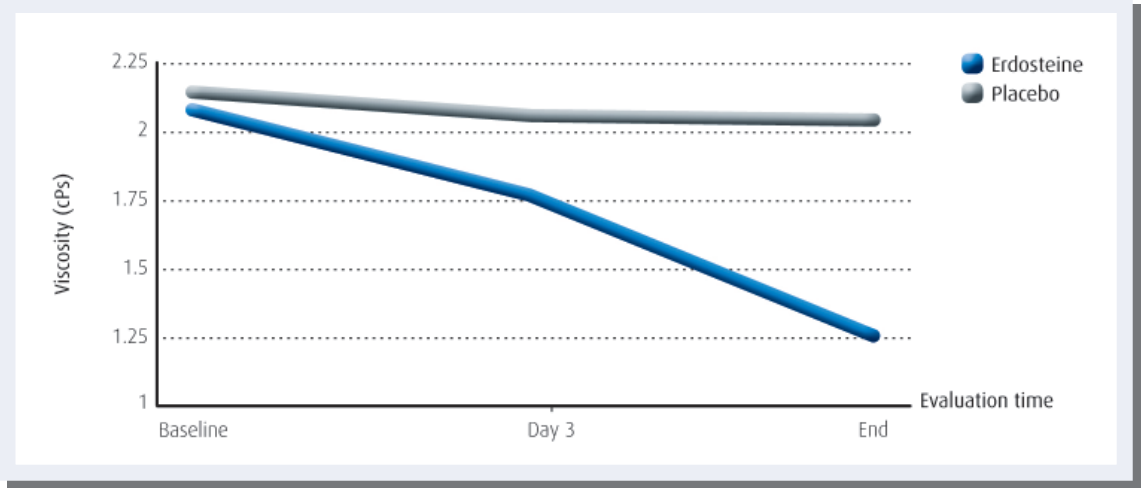
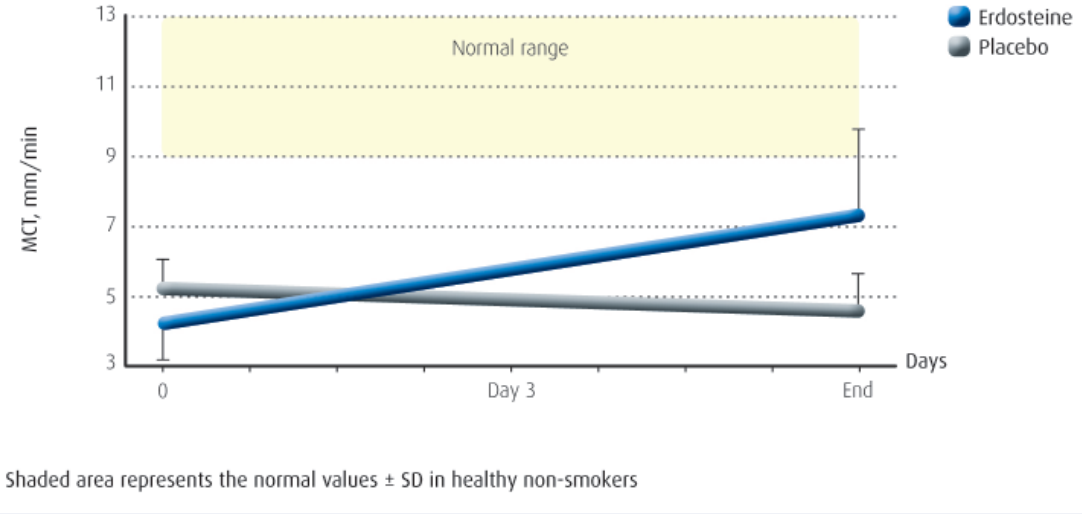


Figure 4. Mean values (±SD) of mucociliary transport (MCT) before and after treatment with Erdosteine or placebo ($p<0.01$)[5].



substantially ROS in peripheral blood: the effect confirmed rapid in onset and proved of maximal extent following a 4-day treatment, while the effect of placebo was absolutely negligible at any time[7].

Furthermore, the reduction in ROS levels observed in the Erdosteine-treated patients is significantly higher at the end of the study (Figure 5)[7].

Polymorphonuclear neutrophils (PMNs) can generate superoxide anions and nitric oxide (NO), which reacting can produce peroxynitrite anions (ONOO-), a potent and potentially toxic oxidant. Also in this case, Met I showed a marked inhibition of the ROS peroxynitrite anions[8].

A study investigated the possible synergistic effect of Budesonide and Met I on the production of harmful oxidants such as peroxynitrites. Chemiluminescence generation during stimulated respiratory bursts of human neutrophils was measured as a marker of ROS production[9]. When the two drugs were combined, there was a greater significant decrease in luminol-amplified chemiluminescence (LACL), indicating a synergistic

Figure 5. Free radical scavenging measured in vitro and vivo[6,7]. Mean integral of luminal-dependent chemiluminescence (LDCL ± SD) of human neutrophils, induced by PMA, associated with Met 1 (*$p<0.05$ vs control) (A). ROS changes measured in Erdosteine and the placebo group of subjects at the different experimental times (*$p<0.01$ vs placebo) (B).

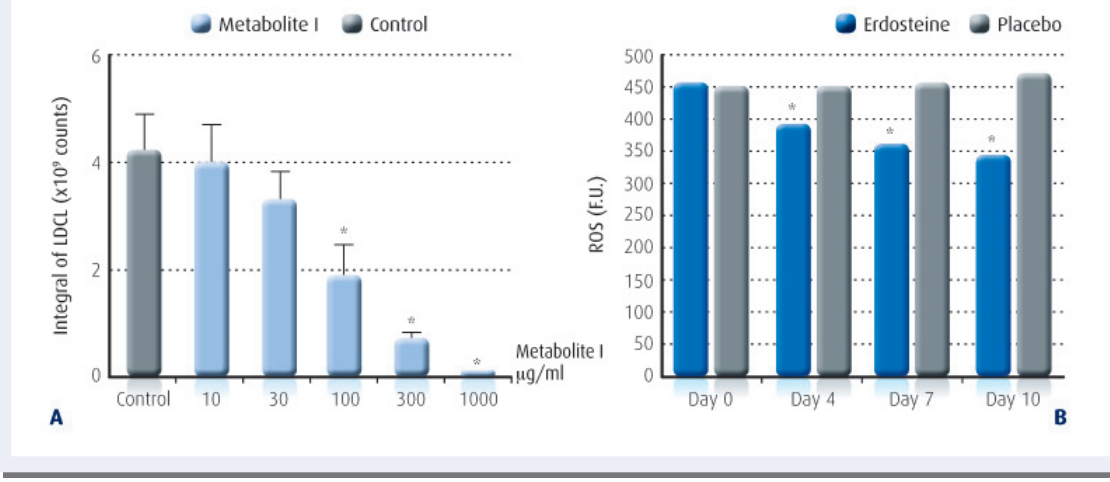
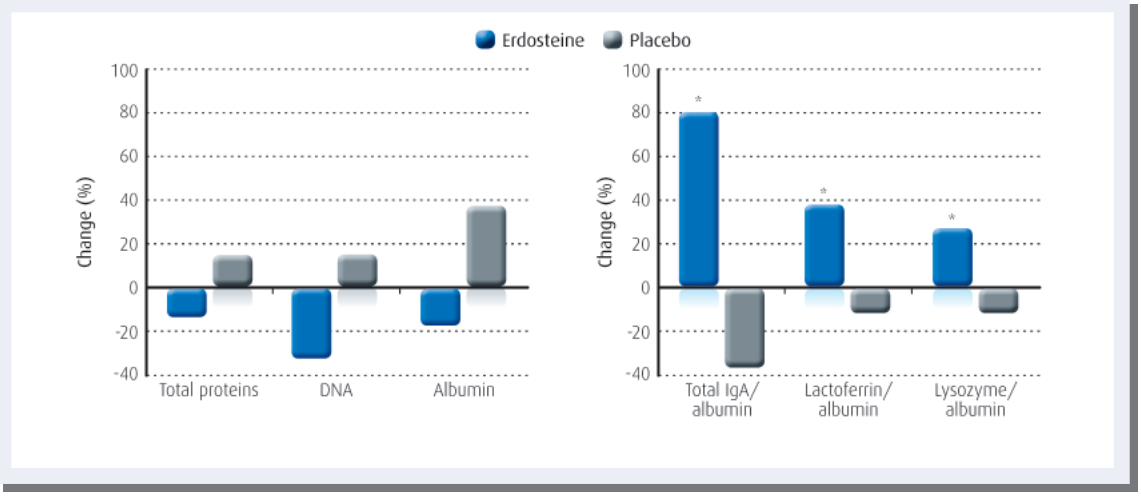


Figure 6. Change in various biochemical properties of sputum after treatment with Erdosteine and placebo ($p \leq 0.05$)[4].



anti-oxidant effect of the two combined drugs, this is of interest for counteracting the airways phlogosis involved in many respiratory diseases.
Erdosteine increases the levels of GSH in plasma and in Broncho-Alveolar Lavage (BAL) fluid. A pilot study in 10 chronic bronchitis patients, showed that levels of GSH increase in the plasma after Erdosteine administration, and are still higher than at baseline after 12 hours, thus maintaining long-term GSH values and related antioxidant activity[10].

In a study with NAC and Erdosteine in chronic bronchitis patients comparing their effect on plasma levels and BAL Fluid levels of GSH[11] the results were in favor of Erdosteine, showing a higher increase in plasma and BAL fluid levels of GSH compared with NAC.

Bronchial anti-inflammatory activity

A placebo-controlled study in patients with clinically stable CB/COPD has shown the effects of Erdosteine on bronchial inflammatory markers[4].
A subsequent double-blind, placebo-controlled, study conducted in 20 current smokers with mild COPD, showed a significant reduction compared to placebo for ROS and Interleukin 8 (IL-8)[7] (Figure 6,7).
The EQUALIFE study, a randomized, double-blind, placebo-controlled, parallel-group, multicenter study, was designed to assess the effectiveness of long-term treatment with Erdosteine in patients with moderate COPD. In the study 155 patients received oral Erdostei-

Figure 7. IL-8 and e-NO change measured in the Erdosteine and the placebo group of subject at the different experimental times ($*p<0.01$)[7].

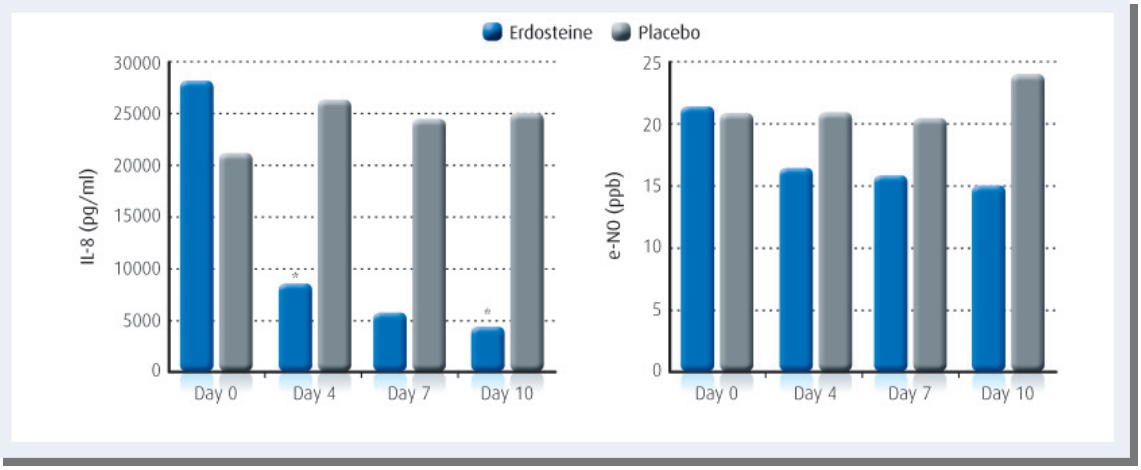
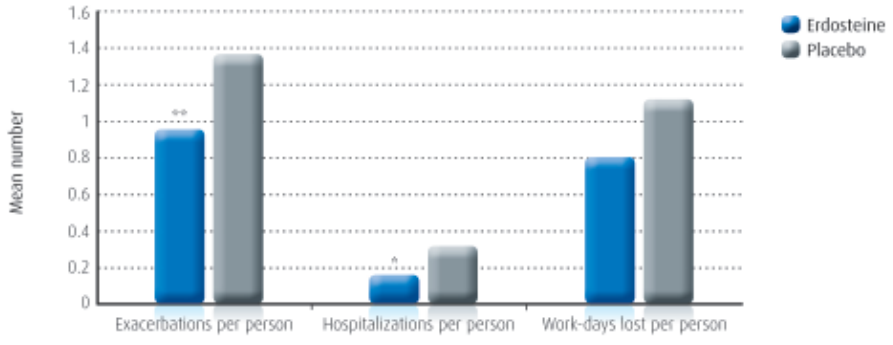


Figure 8. Effects of Erdosteine on patients with COPD[13].



Exacerbations, hospitalization admissions and workdays lost in the Erdosteine and the placebo group (*p<0.05, *p<0.01)

ne, 300 mg bid, or placebo for 8 months during the winter season to evaluate the effect of treatments on exacerbation rates, hospitalization, lung function and quality of life, assessed using the Short Form 36 and the St. George's Respiratory Questionnaire.

A pharmaco-economic analysis was also conducted to compare the two treatments. 124 patients completed the study with Erdosteine (n=63) or placebo (n=61).

The group of COPD patients who received 8 months of continuous treatment with Erdosteine had significantly fewer exacerbations and spent fewer days in hospital than patients receiving placebo. Patients in the Erdosteine group also showed a significant improvement in health-related quality of life. At the end of the treatment period, there was a better performance in the 6-Minute Walk Test (6MWT) and a better lung function (FEV1) in patients treated with Erdosteine. The mean total COPD-related disease costs (direct medical, direct non-medical, and workdays lost) per patient were lower (-30%) in the Erdosteine group than in the placebo group over the study period. The results indicate that 8 months of treatment with Erdosteine is effective in reducing exacerbations and hospitalization rates and in improving health status[12,13] (Figure 8).

Erdosteine induced a reduction of the exacerbation frequency and hospitalisation days. COPD patients treated with Erdosteine experienced a significant improvement in quality of life. Erdosteine is likely to provide an important contribution to the therapy of patients with symptomatic COPD.

Three new scientific evidence have recently proved the pronounced anti-inflammatory activity of Erdosteine.

The first evidence is related to a multicenter pilot post- authorisation study performed in the Czech Republic that was presented first at the 24th Congress of the European Rhinologic Society in Toulouse, France, in June 2012.

This study shows that Erdosteine (600 mg/die) either alone or in combination with topical steroids significantly shrinks the size of nasal polyps as well as reduces subjective complaints of the patients with chronic rhinosinusitis after 3 months of treatment[18].

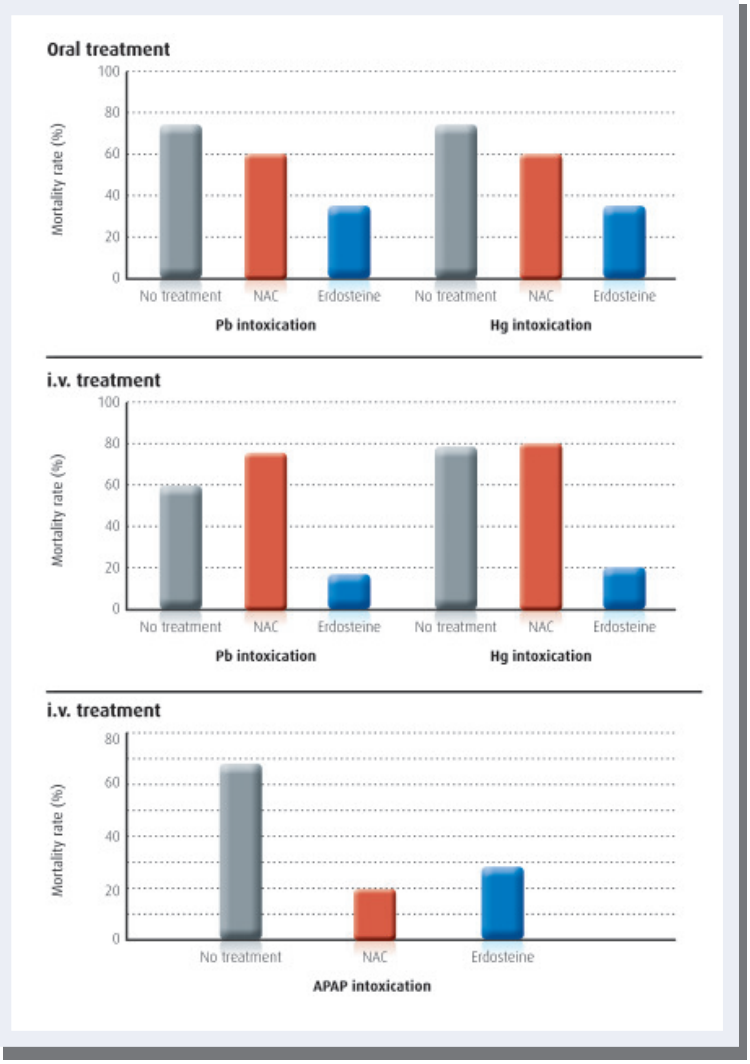
Surprisingly, Erdosteine alone shows an activity comparable to the steroids. This result has a great potential and should be confirmed by further in vitro and in vivo studies.

A second evidence comes from a recent international patent granted to Erdosteine where this drug has shown in animal pharmacology a superior efficacy compared to NAC in the prevention of mortality in acute lead or mercury intoxication and the activity of NAC in paracetamol intoxication[19] (Figure 9).

These models have proven an important organ protection from toxicity that could be highly beneficial in COPD level 4 patients in which are present high levels of ROS and often concomitant other pathologies.

The third evidence indirectly confirms this organ protection effect of Erdosteine in COPD patients. Indeed in 2011 has been published a study showing a cells membrane protection

Figure 9. Efficacy of Erdosteine vs NAC[19].



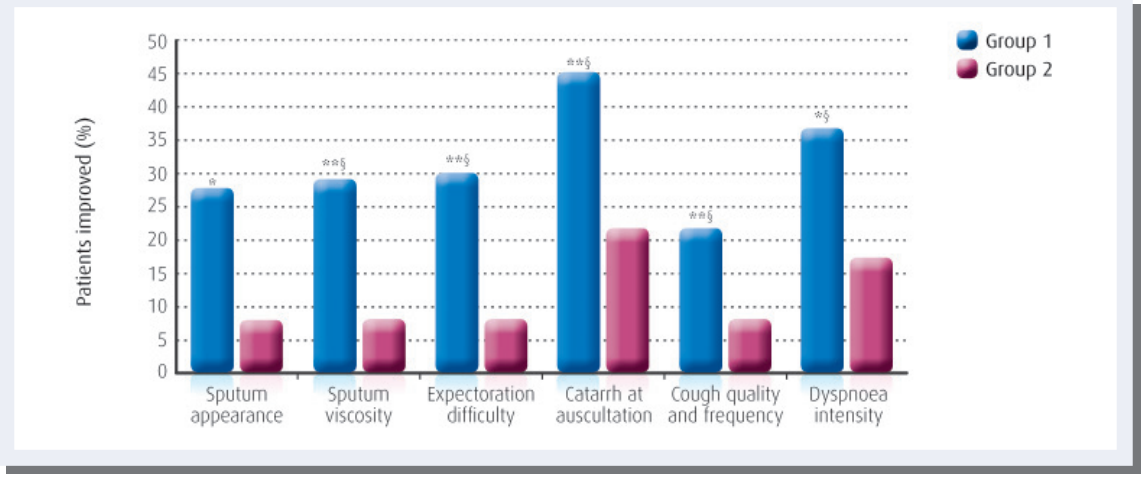
from inflammation performed by Erdosteine in moderate COPD patients[20].
All these recent findings confirm that Erdosteine can play an important role as antinflammatory agent.

Synergism with antibiotics

An international, controlled study (ECOBES, European Chronic Obstructive Bronchitis Erdosteine Study) was conducted on 237 patients with exacerbations of COPD with the aim of showing the synergistc effect of Erdosteine with the antibiotic (group 1 = Erdosteine + Amoxycillin 500 mg tid; group 2 = placebo + Amoxycillin 500 mg tid)[9].
Overall, the clinical response as defined by the GCA (Global Clinical Assessment, comprising sputum appearance and viscosity, expectoration difficulty, catarrh, cough, dyspnoea intensity) was reported to be more favorable and earlier in onset for the Erdosteine group with respect to the placebo group.
Statistically significant improvements vs Amoxycillin monotherapy in GCA parameters occurred after 3-4 days (reduction of 31% vs 22%, respectively) and at treatment end (reduction of 60% vs 40%, respectively at day 7) in the Erdosteine group. Each of the individual components of the CGA also showed a significantly higher improvement. The overall physician and patient judgment of efficacy was in favor of the combination.
The safety profile of Amoxycillin + Erdosteine was comparable to that of Amoxycillin alone.
This study clearly indicates that the clinical picture of infective exacerbations in COPD is modified earlier and to a greater degree by the synergistic activity of Erdosteine and the antibiotic without increasing side effects[9] (Figure 10).
A multicenter, randomized, double-blind clinical study versus placebo was conducted in 200 patients with acute exacerbations of chronic bronchitis[14]. All patients received Ciprofloxacin 500 mg bid and were randomized to Erdosteine or placebo for 7 days. The primary efficacy assessment was a Global Efficacy Index (GEI) consisting of the scores of six parameters (sputum viscosity and appearance, difficulty in expectoration, abnormalities at auscultation, cough and dispnoea).
The Erdosteine group experienced a significantly greater reduction of the GEI at days 3 and 7 compared with the group treated with Ciprofloxacin and placebo. Erdosteine also significantly reduced the 24-hour sputum volume.

Erdosteine improves the efficacy of antibiotic therapy in the treatment of infective exacerbation of COPD.

Figure 10. Improvement of various clinical parameters after treatment with Amoxycillin plus Erdosteine (group 1) or Amoxicliin plus placebo (group 2)[9] (*p<0.02 at days 2-3; **p<0.01 at days 3-4; §p<0.01 at days 8-11).



The synergism with antibiotics has been also confirmed in gastroenterological application. In a prospective, double blind, randomized, placebo controlled study made on 196 patients for the eradication of helicobacter pylori, Erdosteine was add to the standard therapy based on pantoprazole plus Clarithromycin and Amoxicillin. The conclusion was that "Erdosteine significantly increased the success rate of *H. Pylori* eradication treatment consequently we conclude that this agent is an efficient adjuvant therapy that could be used in the first line triple *H. Pylori* eradication regimen"[15] (Figure 11).

Tolerability

Erdosteine is characterized by a placebo like safety profile. More than 2,000 patients have been treated with Erdosteine in clinical studies at doses ranging from 600 to 1,200 mg for a treatment duration from 7 days to 8 months. There were no differences between Erdosteine and placebo in any of the side effect categories: GI, CV, cutaneous and general reactions. The rate of GI side effects of Erdosteine was 3 times lower than that found in patients treated with other mucolytics[16].

A study performed in patients undergoing gastroscopy for pre-existing gastric complaints showed that Erdosteine did not cause any worsening of symptoms, no occurrence of new symptoms or new biological findings[17]. The favorable tolerability profile of Erdosteine is likely to be explained by the presence of blocked sulphydryl groups released only after metabolisation of Erdosteine to Met I. This process occurs, not in the stomach, but when passing into the bowel or after absorption. Specific trials of Erdosteine in geriatric subjects and in patients with mild renal or hepatic failure did not show an impact on adverse reaction rates (Figure 12).

In conclusion due to its multiple mechanism of actions,

Figure 11. Eradication rates of the treatment groups according the PP analysis[15].

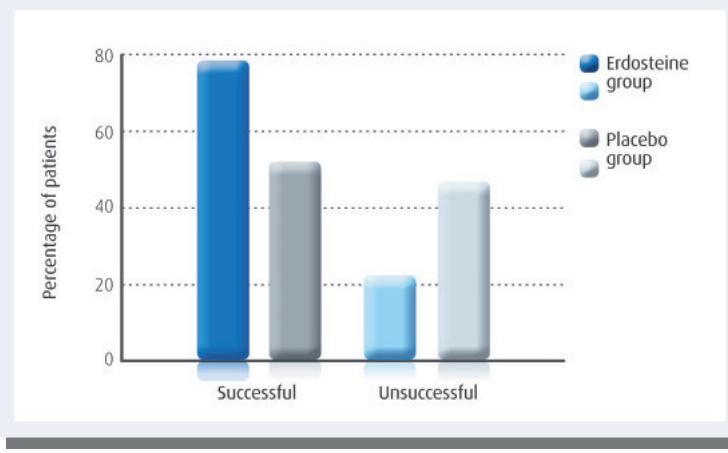
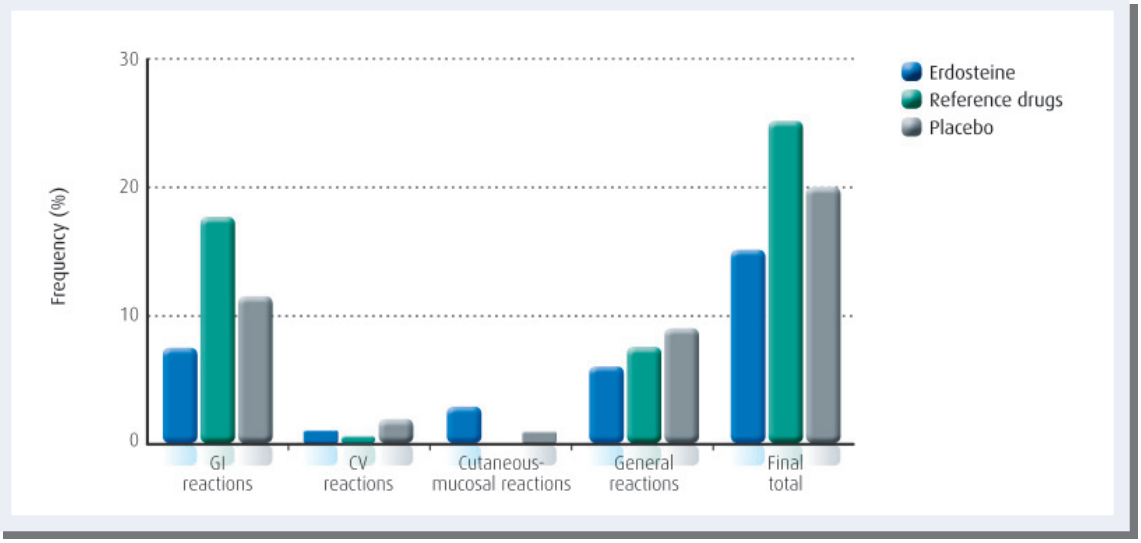


Figure 12. Frequency of adverse reactions with Erdosteine, reference drugs and placebo[16]. (CV= cardiovascular; GI=gastrointestinal).



Erdosteine can be considered one of the most interesting thiol in long term treatment of COPD and its exacerbations. The new findings confirm the potential of this molecule to exceed the PEACE study results and they open an additional space for clinical research to treat patients with resistant infections or comorbidity associated to COPD. TiM

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