

# Highlights-

## Mesalazine in Crohn's disease

12<sup>th</sup> United European Gastroenterology Week  
25–29 September 2004 Prague

### Report overview

- Mesalazine in Crohn's disease: To be or not to be? (28/09/04)  
Chair: Professor Kamm  
Panel: Professor Stange  
Professor Hanauer
- ECCO working group: Consensus report on the management of Crohn's disease (29/09/04)
- BSG guidelines 2004 – Crohn's disease

The use of mesalazines in Crohn's disease (CD) is a topic that is of great interest to gastroenterologists today. The UEGW meeting in Prague in September 2004 provided some great opportunities for attendees to discuss this important topic. The following highlights report focuses on two meetings held at UEGW on recommendations on the treatments of CD.

On Tuesday 28<sup>th</sup> September Ferring sponsored a breakfast meeting where the use of mesalazine in CD was debated by two eminent key opinion leaders, and on Wednesday 29<sup>th</sup> September the public session of the European Colitis and Crohn's Organization (ECCO) reported on the consensus of CD management.

In line with the recommendations of the two reported meetings, the September 2004 BSG guidelines for management of CD are also included.

# Mesalazine in Crohn's disease: To be or not to be?

**A FERRING SPONSORED SYMPOSIUM**

Tuesday 28<sup>th</sup> September

### Summary

As outlined by the chairman, Professor Kamm, the use of mesalazines in Crohn's disease (CD) is an extremely important, yet controversial, clinical topic. This symposium consisted of a lively debate between two distinguished gastroenterologists, Professor Stange of Robert-Bosch-Krankenhaus, Germany, and Professor Hanauer of The University of Chicago Pritzker School of Medicine, USA, with opposing views on the use of mesalazine in CD. Audience voting (among approximately 300 delegates) showed that, contrary to Professor Stange's beliefs, the majority of the audience supported the use of mesalazines in CD.



### Introduction

**Professor Kamm, St Mark's Hospital, UK**

Professor Kamm opened the meeting by establishing that there is no reason for debating the use of mesalazine in ulcerative colitis (UC).

As early as 1960's, mesalazine had a clear role in the treatment of UC. He described how the efficacy of sulphasalazine compared with

placebo in maintaining remission in UC was demonstrated in a landmark study by Misiewicz et al (1965), after which the long-term use of sulphasalazine was recommended. However, owing to the high incidence of adverse events associated with sulphasalazine, newer non-sulpha containing mesalazines, which have a far better side effect profile, are now widely used.

While the use of mesalazine for inducing and maintaining remission in UC is established, its use in CD remains controversial. In this debate we heard arguments from two eminent gastroenterologists with opposing views on the benefits of mesalazine for inducing and maintaining remission in CD.



# Mesalazine to be used in Crohn's disease

Professor Hanauer, University of  
Chicago, USA

*'Prescriptions are written  
on paper, not in stone.  
Advance to more potent,  
more toxic agents if the  
patient does not respond  
to mesalazine, or if  
recurrence occurs'*

*Professor Hanauer*

## Interview with Professor Hanauer

*Professor Hanauer was interviewed after his exciting presentation to ascertain his views on the use of mesalazine in the treatment of CD. He uses mesalazines (always 4g/day) in the treatment of mild/moderate disease and believes there are positive data to support the use of higher doses (up to 7g/day) without dose-related side effects. Professor Hanauer believes that the mesalazine dose required to induce remission should be continued as maintenance therapy.*

Professor Hanauer opened his presentation by stating that, in his opinion, a combination of evidence *and* experience provides compelling evidence to demonstrate that mesalazines do have a therapeutic role in CD. He indicated that the majority of patients with CD are either in clinical remission or have mild/moderate disease.

- For induction of remission in CD, Professor Hanauer outlined how several studies have demonstrated that the rate of mesalazine-induced remission is consistently superior to that of placebo and equal to that of 6-mercaptopurine [6MP] for maintenance.
- Professor Hanauer reiterated that in their meta-analysis (Hanauer and Strömberg, 2004), PENTASA\* 4g/day was demonstrated to be significantly better than placebo ( $p=0.04$ ) in reducing CDAI in active CD. Professor Hanauer pointed out that in every one of the three studies included, PENTASA was better than placebo. However, the placebo rates varied and, in two of the three studies, a significant difference was not observed, despite consistent response rates for mesalazine.
- In response to the claim that pharmaceutical companies only publish positive data, Professor Hanauer described how, on the contrary, the meta-analysis discussed was rejected in the early 2000's because the publishers considered this to be a 'negative trial'.
- Professor Hanauer showed data demonstrating lack of steroid efficacy in maintenance therapy. Only 25% of patients remain in remission after 12 months therapy. Thus, following steroid-induced remission, other, more toxic, agents are required to maintain remission.
- Professor Hanauer, based on the established long-term safety profile of these agents, advocated mesalazine as first-line therapy to induce and maintain remission. Only if these agents fail should other, more toxic, therapies such as steroids, antibiotics and infliximab, be considered.
- During his speech, Professor Hanauer also referred to the newly released British Society of Gastroenterology (BSG) guidelines, discussed elsewhere in this report, supporting his recommendation.

# Mesalazine not to be used in Crohn's disease

Professor Stange, Robert-Bosch-Krankenhaus, Germany

Professor Stange believes that there is no consistent evidence to support the use of mesalazine in CD. The use of ciclosporin A in CD is not advocated on the basis that, despite demonstrated efficacy in one study, three subsequent studies failed to demonstrate any statistically significant benefit over placebo. However, Professor Stange stated that despite a similar scenario for mesalazine in CD, the use of these agents is widespread.

- Professor Stange described how the Singleton study (1993) showed a dose-response effect (4g/day) for mesalazine (PENTASA\*) in inducing remission. However, Professor Stange proceeded to outline several subsequent trials which he considers to have failed to demonstrate such a benefit. In the treatment of acute CD, mesalazines have not demonstrated superior efficacy compared with steroids or antibiotics. When also considering the two unpublished studies, mesalazines have not demonstrated clinically relevant efficacy superior to placebo.
- A recent meta-analysis (Hanauer and Strömberg, 2004), demonstrated a Crohn's disease activity index (CDAI) decrease of  $-18$  ( $p=0.04$ ) with mesalazine (PENTASA) versus placebo, which equates to a reduction frequency of 1.3 stools/day. Professor Stange questioned whether this reduction is clinically relevant. In addition, he speculated that the two studies of the meta-analysis, which failed to demonstrate statistical superiority of mesalazine, were not published in order to withhold negative data.
- In terms of maintaining remission, mesalazine is a treatment option if remission has been achieved medically. However, according to a meta-analysis by Camma et al (1997), there is no consistent evidence for its efficacy.
- Professor Stange presented the very new ECCO consensus on treatment, agreeing to the usage of mesalazine only in certain situations. He emphasized the role of local or systemic corticosteroids in acute disease as well as the benefit from immunosuppression in maintenance treatment. The ECCO consensus defines the role of both aminosaliclates and steroids:
  - Mildly active, localised ileocaecal CD; budesonide 9 mg/day is the preferred treatment. The benefit of mesalazine is limited.
  - Colonic CD; may be treated with aminosaliclates if only mildly active, or with systemic steroids.

*'The widespread use of mesalazine does not prove its efficacy'*

*Professor Stange*

## Interview with Professor Stange

*After his presentation, Professor Stange explained his views on the use of mesalazines in CD. For mild/moderate ileocaecal CD he uses budesonide alone as he does not believe there is evidence to support the use of combination therapy. For maintenance therapy, Professor Stange uses azathioprine (AZA) as monotherapy.*

# Discussion – 'Right to respond'



## Audience Interviews

### Professor Hanauer

- One of the biggest problems with CD is its remitting/relapsing disease course. Budesonide is not effective long-term. A relapse rate of 80% occurs after one year of therapy. However, we have the ability to maintain patients with mild/moderate CD with mesalazine.
- If patients did not respond to mesalazine we wouldn't use it. We are voting with our feet and our prescription pads. Physicians need to learn to extrapolate findings from clinical trials to clinical practice.

### Professor Stange

- Response rates are not important because they depend on the activity of the disease. This is why placebo response rates vary between studies as has been discussed today. It is the difference between treatment groups that matters. Number needed to treat (NNT) values are the most accurate estimate of a drug's efficacy in inducing and maintaining remission. Therefore, remission rates for all three trials included in the meta-analysis are required to determine the true efficacy of mesalazine.

### Question from audience

(Dr Lachter, Israel):

**Query:** What is the incidence of adverse events associated with mesalazine therapy?

**Response:** There are a few mild side effects, such as headaches and, very rarely, nephrotoxicity, although the latter is idiosyncratic. Both experts agree that the side effect profile of mesalazine is not an issue in discouraging the use of mesalazine in CD.

*'The use of high dose (4g/day) mesalazines (PENTASA and SALOFALK<sup>†</sup>) in the treatment of mild/moderate CD is supported, with continued high dosage as maintenance therapy'.*

**Josef Salac and Karel Malik, Czech Republic;  
Fernandez Blanco Herranz, Spain**

*'I advocate the use of PENTASA (3–4g/day) as first line therapy in mild/moderate CD, as it is effective and easy to take; doses vary depending on the patient but high doses (4g/day) are useful and safe'.*

**Jan Teuwen and Henri Büscher, Belgium**

*'In my experience, the use of PENTASA 4g/day is effective and safe for the treatment of mild/moderate CD'.*

**Daniel Ginard, Spain**

*'More clinical data are required to convince me of the efficacy of mesalazines in CD; I currently use prednisolone and an elemental diet as therapy for mild/moderate CD'.*

**Vaidotas Urbonas, Lithuania**

*'Mesalazine is effective for the treatment of colonic CD; I use 3–6g/day to induce remission. I use mesalazines as maintenance therapy for Crohn's colitis, I taper down the dose to a minimum of 3g once remission is achieved'.*

**Gerald Fraser, Israel**

*'Mesalazines, such as PENTASA, are effective at high doses (4g/day) in the treatment of mild/moderate CD. I often use mesalazine in combination with other drugs such as AZA<sup>§</sup> or infliximab as maintenance therapy'.*

**Dag Risberg, Sweden**

<sup>†</sup>SALOFALK is a trademark of Dr. Falk  
<sup>§</sup>AZA is a trademark of GSK

# ECCO working group: Consensus report on the management of Crohn's disease

Wednesday 29th September

The European Colitis and Crohn's Organization (ECCO) gathered prior to the UEGW on 24–25 September to discuss European guidelines on the management of CD (publication expected early 2005). The recommendations were based on evidence (literature) and experience (questionnaires). The ECCO consensus found a place for the use of mesalazine in CD, as outlined below:

#### In general:

- Treatment recommendations depend on the disease site, activity, behaviour, course (frequency of relapse), previous response to therapy, side effect profile, and presence of extraintestinal complications.
- Patients should be encouraged to participate actively in decisions regarding their treatment.

#### Consensus on the use of mesalazine in the management of active CD:

- *Colonic CD* may be treated with aminosalicylates if only mildly active, or with systemic steroids.
- For mild active *localised ileocaecal CD*, budesonide is the preferred treatment. The benefit of mesalazine is limited.

#### Consensus on the use of mesalazine in the maintenance of remission:

- If remission has been achieved medically, maintenance with mesalazine is a treatment option, although there is no consistent evidence for its efficacy.
- Prophylaxis is recommended after surgery; the drug of choice is mesalazine >2 g daily.

## British Society of Gastroenterology (BSG): Guidelines for the management of inflammatory bowel disease in adults, Carter et al (2004), on behalf of the IBD section of the BSG.

A new guideline for the treatment of IBD has recently been published by the BSG. These guidelines provide an evidence based document describing good clinical practice for investigation and treatment. The guidelines for the treatment of active CD and maintenance of remission in CD are outlined below:

Crohn's disease activity	Recommended therapy
<b>Acute (ileal/ileocolonic/colonic disease)</b>	<ul style="list-style-type: none"><li>• In mild ileocolonic CD, high dose mesalazine (4 g daily) may be sufficient initial therapy.</li><li>• For patients with moderate–severe CD, or those with mild–moderate ileocolonic CD that has failed to respond to oral mesalazine, oral corticosteroids, such as prednisolone 40 mg daily, may be appropriate.</li></ul>
<b>Maintenance</b>	<ul style="list-style-type: none"><li>• Mesalazine<sup>†</sup> has limited benefit and is ineffective at doses &lt;2 g/day, or for those who have needed steroids to induce remission.</li><li>• All smokers should be strongly advised to stop, with help (counselling, nicotine patches or substitutes) offered to achieve this.</li></ul>

<sup>†</sup>Sulphasalazine is generally not recommended due to higher incidence of adverse events compared with newer mesalazine drugs

## Questions from the audience:

Dr Thomsen from Denmark commented that, regarding the use of mesalazines for acute disease and maintenance of remission in CD, he was disappointed that the organization had not been more critical of the data and what he considers to be 'publication bias'.

Dr Travis from the UK responded that, in the recent Hanauer and Strömberg meta-analysis, the relative decrease in CDAI of 18 of mesalazine versus placebo, although statistically significant, may not be clinically relevant.

However, Dr Travis acknowledged that other data from randomized controlled trials demonstrate that mesalazines have a statistically significant benefit over placebo. Therefore, the use of mesalazine is justified in some circumstances.

Ferring emphasised that in the intent-to-treat population the decrease with mesalazine was 63. Furthermore, in the per-protocol population the overall decrease was 83 in the mesalazine group.

# Ferring – Dedicated to Gastroenterology

Founded in 1950, Ferring was one of the early companies to develop pharmaceutical products based upon naturally occurring pituitary peptide hormones

Ferring is a privately held company which produces pharmaceutical products enabling doctors to treat patients on the body's own terms.

Ferring is a speciality, research-driven biopharmaceutical company that identifies, develops and markets innovative products. Ferring works within the following therapeutic areas: urology, gastroenterology, gynaecology and endocrinology.

Ferring was one of the first in the world to produce synthetic peptides on a commercial scale. Today, the expertise and technologies in these compounds makes the company a key player in the field of peptide and protein chemistry. The peptide, promoted under the trademark GLYPRESSIN\* (terlipressin) was developed for bleeding oesophageal varices.

However, Ferring's history is not limited to peptide-based products. Ferring scientists have developed other medicines, including PENTASA, a unique ethylcellulose coated microgranule formulation of mesalazine for patients suffering from ulcerative colitis and Crohn's disease.

Ferring started in Sweden in 1950 as a small company, but is now operating globally. Today, the company employs about 2,400 people in some 40 countries.



Both the corporate organisation, as well as the production facilities, have been streamlined and upgraded for the new millennium. The headquarters in Lausanne, Switzerland, is expanding and will host a number of the company's global functions from January 2006.

Ferring invests heavily in research and development to ensure a future flow of new and innovative products. Major R&D projects are ongoing, which will complement Ferring's existing product portfolio.

## History of PENTASA

### From small beginnings to world-wide use

Since the late 1980s, PENTASA has taken a unique place in the Ferring product portfolio. As an effective drug for the treatment of inflammatory bowel diseases, PENTASA is now sold in more than 50 countries around the world and is considered a key Ferring product.

Ferring Managing Director, Ole Kjerulf-Jensen, remembers the day in 1978 when he and co-founder Eva Paulsen discussed an article featuring scientists in South Africa crushing medications for use in enemas. At that time, one of the only treatments available

for IBD contained sulphapyridine (SP) which, when taken orally, was known to cause side effects.

'We knew that the active chemical 5-ASA split in the large colon from the SP and maybe it would be possible to contain it,' said Kjerulf-Jensen. In 1979, Eva Paulsen found, in an article in the BMJ, that researchers in the UK were able to separate out 5-ASA, and she instructed researcher Søren Halskov to investigate the possibilities.

'We knew that straight 5-ASA could be

absorbed directly into the gut with great possibilities', said Søren Halskov. 'It was a novel idea and we began to think about how we could use this data to our advantage.'

Ferring continues to search for new therapies that not only alleviate symptoms, but also attack the underlying causes of these diseases.

For further information please contact your local Ferring representative, or visit [www.ferring.com](http://www.ferring.com).

