5-ASA in Modern Era IBD Management

Siavosh Nasseri-Moghaddam MD, MPH, AGAF
Associate Professor of Medicine
DDRI, TUMS

Shahrivar 28, 1404 (September 19, 2025)
Rossen-Darman (Tillots Pharma) Seminar
Espinas Hotel, Tehran, Iran

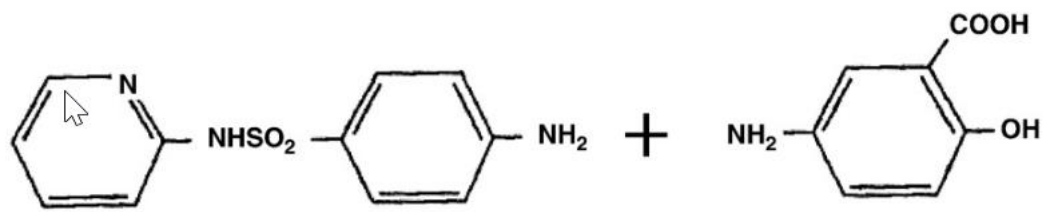
Background

- The 1st disease-specific, targeted, therapeutic agents of the 20th century
- 1932: Prontosil Rubrum was found by Bayer scientist as an antibacterial medication
- 1935: Sulfanylamide found to be the active ingredient of Prontosil Rubrum → Purified and a colorless substance isolated

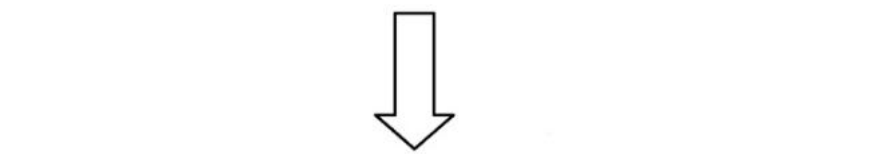


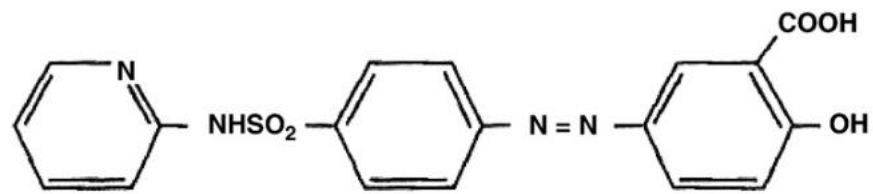
Background

- This was done with the belief that RA was considered to be due to a bacterial infection (at least partly)
- During studies at Karolinska, Nana Svartz, rheumatologist & the 1st woman to become Professor of Medicine in Sweden, incidentally tried it in 9 patients with UC and reported the results in 1942
- Deaths due to “yellow liver atrophy” were reported and a search for an agent with Rxc effects of sulfanilamide but w/o its toxicity was started
- Salicylazosulfapyridine or Salazopyrin was the best candidate
- May and Baker 693 (sulphapyridine) was later developed which was then combined with 5-ASA to make Sulfasalazine



SP 5ASA





SASP

The 1st controlled trial of sulfasalazine in UC

ORIGINAL ARTICLES · Volume 285, Issue 7378, P185-188, January 23, 1965 Download Full Issue

CONTROLLED TRIAL OF SULPHASALAZINE IN MAINTENANCE THERAPY FOR ULCERATIVE COLITIS

J.J. Misiewicz, M.B., B.Sc. Lond. · J.E. Lennard-Jones, M.B. Cantab., M.R.C.P. · A.M. Connell, M.B. Glasg., M.R.C.P.E. [1] · J.H. Baron, D.M. Oxon., M.R.C.P. · F. Avery Jones, M.D. Lond., F.R.C.P.

Affiliations & Notes Article Info

24 of 34 patients on 2g SPS maintained in remission at 1 year

Gut, 1973, **14**, 923-926

A controlled therapeutic trial of long-term maintenance treatment of ulcerative colitis with sulphasalazine (Salazopyrin)

A. S. DISSANAYAKE AND S. C. TRUELOVE

From the Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford

SUMMARY Sixty-four patients with proven ulcerative colitis who had been maintained on sulphasalazine as their sole form of treatment for a minimum period of one year were entered into a controlled trial of sulphasalazine versus dummy tablets for a period of six months. All the patients admitted were not only symptom-free but also showed no evidence of inflammation on sigmoidoscopy and rectal biopsy. A patient was judged to have relapsed when there was a recurrence of colitic symptoms accompanied by sigmoidoscopic and histological evidence of inflammation.

The patients who received dummy tablets had more than four times the relapse rate of those receiving sulphasalazine. The results were similar in patients who had been on maintenance treatment with sulphasalazine for less than three years before entry into the trial and in those who had been on this treatment for more than three years.

It is concluded that maintenance treatment of ulcerative colitis with sulphasalazine should be continued indefinitely unless contraindicated by side effects.

- The concept that life-long therapy was central to the successful treatment of this condition was introduced
- Now, with long-term preventive Rx becoming standard, the problem of side effects became one of the driving factors behind the search for which part of the molecule was responsible for sulfasalazine’s anti-inflammatory activity.

Clinical Trial > Lancet. 1977 Oct 29;2(8044):892-5. doi: 10.1016/s0140-6736(77)90831-5.

An experiment to determine the active therapeutic moiety of sulphasalazine

A K Azad Khan, J Piris, S C Truelove

PMID: 72239 DOI: 10.1016/s0140-6736(77)90831-5

Abstract

Sulphasalazine (S.A.S.P.) is of proven value in the treatment of ulcerative colitis, but its mode of action is unknown. When it is taken by mouth, nearly all the dose reaches the colon intact, where it is split by bacteria into sulphapyridine (S.P.) and 5-aminosalicylic acid (5-A.S.A.). An experiment was devised to determine whether the therapeutic property of S.A.S.P. is a function of the parent molecule or of these two principal metabolites. Retention enemas of S.A.S.P., S.P., and 5-A.S.A. were administered to volunteer patients with sigmoidoscopic evidence of active ulcerative colitis. The experiment was conducted as a blind controlled therapeutic trial, each patient having one of the test enemas daily for two weeks. Pronounced histological improvement was observed in approximately 30% of the patients receiving S.A.S.P. or 5-A.S.A., and in only 5% of those receiving S.P. It is concluded that the active therapeutic moiety of S.A.S.P. IS 5-A.S.A. and that the S.P. functions as a carrier ensuring that the 5-A.S.A. is liberated within the colon.

- Azad Khan and Sidney Truelove performed an elegant series of studies using three separate retention enemas in a blind clinical study over a period of two weeks.
- Sulfasalazine and 5 aminosalicylate (5-ASA) enemas produced a significant clinical improvement in 30% of patients compared with a 5% response in those who received sulfapyridine

New Questions

- The problem with 5-ASA is its lack of stability.
- Solutions to this problem have centred around three main approaches:
  - delivery directly to the colon as a retention or foam enema;
  - encapsulating the drug within a pharmaceutical coating;
  - binding the 5-ASA moiety to a carrier molecule.
- Sidney Truelove's group investigated the effect of two 5-ASA molecules linked back to back
  - The resulting compound was disodium azodisalicylate or Olsalazine.
  - Although effective, its role has been limited by the occurrence of diarrhea as a significant side effect.

- During the 1980s John Rhodes and Brian Evans investigated the role of eudragit-S coating as a way of stabilising mesalazine.
  - Their novel idea was to develop a product which would split open with the change in pH as intestinal content crossed the ileocaecal valve into the colon
  - The rupture of the outer capsule released active mesalazine into the colon.
  - The product was marketed as Asacol by Tillotts Laboratories Ltd.

Br. J. clin. Pharmac. (1983), **16**, 185–187

COLONIC RELEASE OF 5-AMINO SALICYLIC ACID FROM AN ORAL PREPARATION IN ACTIVE ULCERATIVE COLITIS

M.J. DEW, R.E.J. RYDER, N. EVANS, B.K. EVANS & J. RHODES
Departments of Gastroenterology and Pharmacy, University Hospital of Wales, Cardiff CF4 4XW

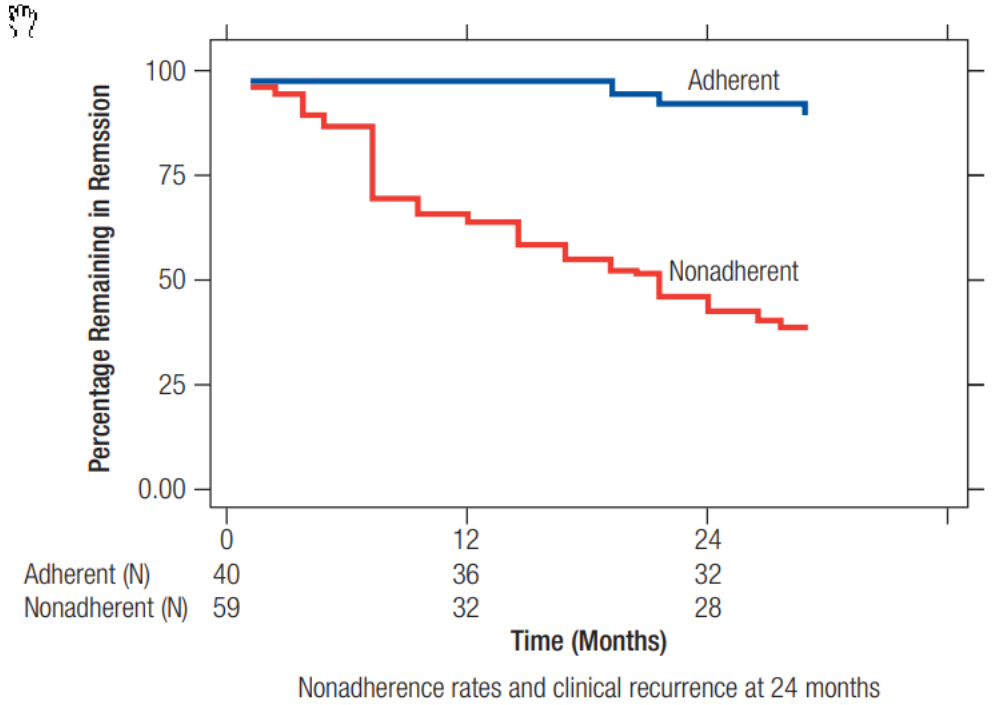
5-amino salicylic acid coated with acrylic based resin was given orally to eight patients with active ulcerative colitis. Abdominal X-rays confirmed that the preparation released its contents in the terminal ileum and proximal colon. Differences between individuals were marked; the plasma 'concentration-time profile' reflected variations in the time taken for tablets to reach the terminal ileum.

Keywords 5-amino salicylic acid colonic release ulcerative colitis

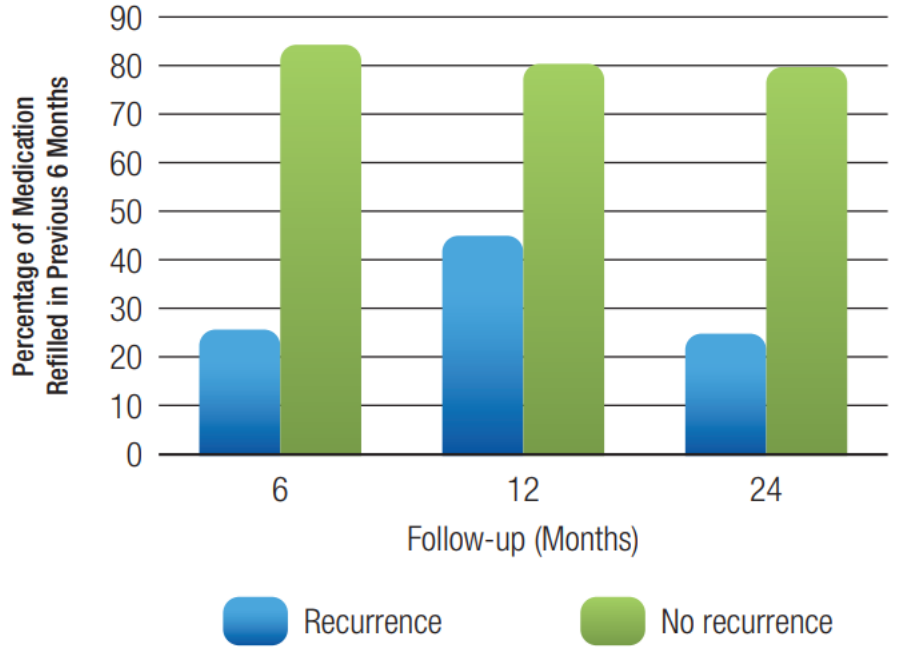
Further techniques

- Eva Paulsen, a civil engineer specializing in pharmaceuticals, late 1970s:
  - encapsulating mesalazine within microgranules, prolonged release through coating made from alchyl-cellulose, independent of the pH. The product was marketed as Pentasa
- In 198s, linking the 5-ASA moiety to an inert carrier molecule
  - production of two compounds with branch chains containing an amino acid
    - 4-aminobenzoyl-β-alanine or Balsalazide
    - Glycine chain or Ipsalazide
- Balsalazide has been shown to be effective in a large number of clinical trials.
  - It probably has other modes of action as well
- Early 1980s the search for better stability and less side effects led to an interest in 4-ASA rather than 5-ASA, always as an enema
  - It appears as effective as 5-ASA with fewer side effects
  - Commercially available as Quadrasa in a number of European countries

Compliance



Nonadherence rates and clinical recurrence at 24 months



Adapted from Kane et al 2003

Now the issue of compliance!

- Attempts to develop a once daily preparation
- The multimatrix 5-ASA
- OPTICORE™:
  - Combines two release triggers (pH and enzyme: Phloral™) in the outer layer, with an inner layer promoting a release acceleration mechanism (Duocoat™).
  - The technology comprises an inner layer of partially neutralized enteric polymer with a buffer agent and an outer layer of a mixture of Eudragit® S and resistant starch.

Indications in modern era

- Induction or maintenance of remission for mild-to-moderate ulcerative colitis.
  - Topical mesalamine stands as the first-line treatment for this condition
  - Suppository for disease localized to the rectum
  - Enemas for disease up to the sigmoid colon
  - Topical 5-ASAs preferred over topical glucocorticoids
- A combination of rectal 5-ASA with oral 5-ASA is recommended for extensive mild-to-moderate ulcerative colitis.
  - Combining oral and rectal 5-ASA achieves higher rates of induction and maintenance of remission, avoiding escalation to corticosteroids or immunosuppression

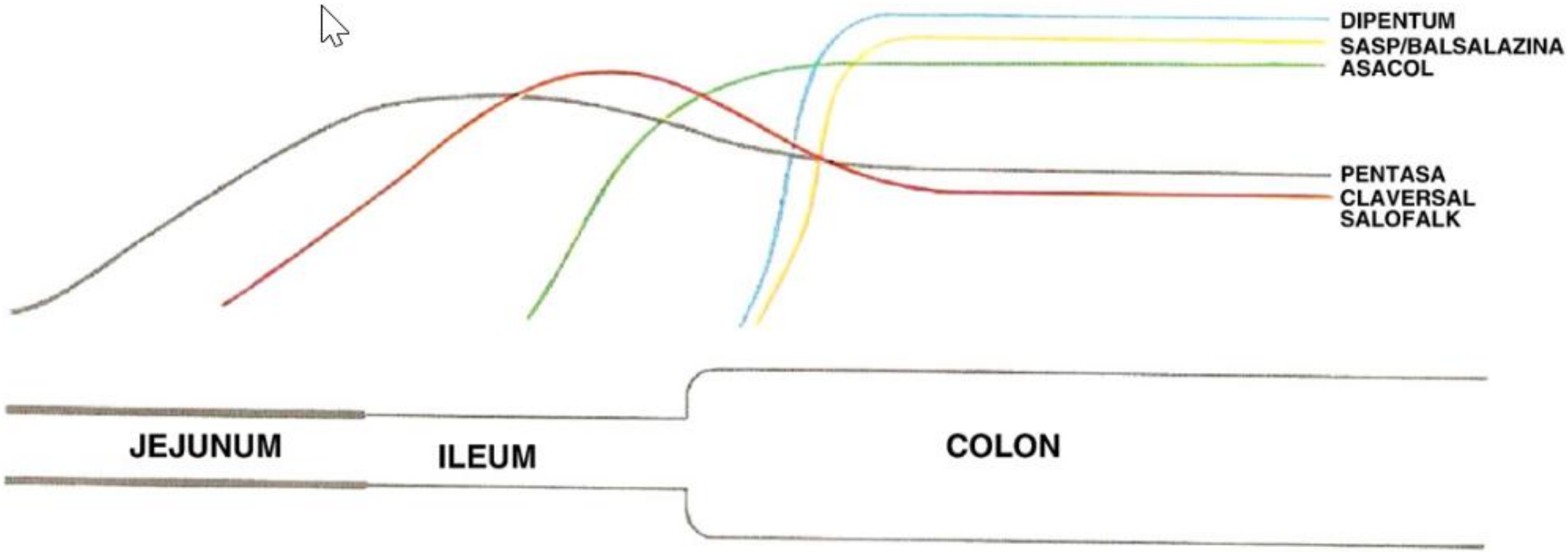
Induction and Maintenance of UC, ACG 2025

- In patients with mildly to moderately active ulcerative proctitis, we recommend rectal 5-aminosalicylate acid (5-ASA) therapies at a dose of 1 g/daily for induction of remission (Strong recommendation, moderate quality evidence).
- In patients with mildly to moderately active proctitis or left sided colitis, we recommend rectal 5-ASA enemas at a dose of at least 1 g/daily preferred over rectal steroids for induction of remission (Strong recommendation, moderate quality of evidence).
- In patients with mildly to moderately active left-sided UC, we suggest rectal 5-ASA enemas at a dose of at least 1 g/daily combined with oral 5-ASA at a dose of at least 2.0 g/daily compared with oral 5-ASA therapy alone for induction of remission (Conditional recommendation, low quality of evidence).
- In patients with mildly to moderately active extensive colitis, oral 5-ASA at a dose of at least 2.0 g daily is recommended to induce remission (Strong recommendation, moderate quality of evidence).

Induction and Maintenance of UC, ACG 2025

- In patients with mildly to moderately active UC who fail to reach remission with appropriately dosed 5-ASA (at least 2–4.8 g daily oral mesalamine and/or at least 1 g daily rectal mesalamine), we suggest against changing to an alternate 5-ASA formulation to induce remission. Alternative therapeutic classes should be considered (Conditional recommendation, low quality of evidence).
- In patients with mildly active UC of any extent, we suggest using a low dose (2.0–2.4 g) of 5-ASA, in comparison with a higher dose (4.8 g), because there is no difference in remission rate (Conditional recommendation, very low quality of evidence).
- In patients with mildly to moderately active UC of any extent using 5-ASA to induce remission, we recommend either once daily or more frequently dosed oral 5-ASA based on patient preference to optimize adherence because efficacy and safety are no different (Strong recommendation, moderate quality evidence).
- In patients with mildly active ulcerative proctitis, we recommend rectal 5-ASA at a dose of 1 g daily for maintenance of remission (Strong recommendation, moderate quality of evidence).
- In patients with mildly active left-sided or extensive UC, we recommend oral 5- ASA therapy (at least 1.5 g/d) for maintenance of remission (Strong recommendation, moderate quality of evidence).
- In patients with prior moderately to severely active UC who have achieved remission but previously failed 5-ASA therapy and are now on anti-TNF therapy, we suggest against using concomitant 5-ASA for efficacy of maintenance of remission (Conditional recommendation, low quality of evidence).

	Mild[a]	Moderate	Severe[b]
(1) Frequency of defection	4 Times or less	Intermediate between mild and severe	6 Times or more
(2) Bloody stool	(–) or (+)		(+++)
(3) Fever[c]	Absent		37.5°C or higher
(4) Tachycardia[d]	Absent		90/min or more
(5) Anemia	Absent		Hb 10 g/dL or less
(6) ESR	Normal		30 mm/h or more


DIPENTUM
SASP/BALSALAZINA
ASACOL
PENTASA
CLAVERSAL
SALOFALK
JEJUNUM
ILEUM
COLON

Mechanism of action

- The exact mechanism of 5-ASA is unknown
- Hypothesis: modulation of the inflammatory response derived from the cyclooxygenase and lipooxygenase pathways, decreasing the synthesis of prostaglandins and leukotrienes
- Other potential mechanisms:
  - Interference with the production of inflammatory cytokines via:
    - Reducing the activity of nuclear factor κB (NF-κB) and
    - Inhibition of tumor necrosis factor (TNF),
    - Inhibition of cellular functions of mucosal lymphocytes, macrophages, and natural killer cells
    - Also postulated as a free radical scavenger and an antioxidant

- The oral formulation of 5-ASA is available as:
  - delayed-release capsules (400 mg),
  - extended-release capsules (250 mg, 375 mg, and 500 mg), and
  - delayed-release tablets (800 mg and 1200 mg)
  - *5-ASA delayed-release capsules and tablets are NOT therapeutically equivalent*
- Can be taken w or w/o food
- Do not cut, chew, or crush 5-ASA extended-release products

Thank you
Simple questions are welcome!

