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Month/Year of Review: September 2012 **Date of Last Review:** September 2010
PDL Class: Aminosalicylates (Drugs for Ulcerative Colitis) **Source Document:** Provider Synergies

Current Status of PDL Class:

- Preferred Agents: MESALAMINE CAPSULES ER 24H (APRISO®), MESALAMINE TABLET DR (ASACOL®), MESALAMINE ENEMA, MESALAMINE WITH CLEANSING WIPES KIT, OLSALAZINE SODIUM CAPSULE (DIPENTUM®), SULFASALAZINE TABLET DR, SULFASALAZINE TABLET
- Non-preferred Agents: BALSALAZIDE, MESALAMINE TABLETS DR HIGH DOSE (ASACOL HD®), MESALAMINE TABLETS MMX (LIALDA®), MESALAMINE CAPSULES (PENTASA®), MESALAMINE ENEMAS SULFITE-FREE (SFROWASA®), MESALAMINE SUPPOSITORIES (CANASA®)

Previous Recommendations:

1. Evidence does not support a difference in efficacy/effectiveness between the aminosalicylates.
2. Evidence does not support a difference in harms/adverse events between the aminosalicylates.
3. Olsalazine can cause secretory diarrhea and is only indicated for maintenance therapy.
4. Mesalamine MMX (Lialda®) and Mesalamine extended release capsules (Apriso™) have no long term studies.
5. Mesalamine MMX (Lialda®) and Mesalamine capsules (Pentasa®) are only indicated for mild to moderate ulcerative colitis.

PA Criteria/QL: The generic non-preferred drugs in PDL classes Prior Authorization is in place to support preferred PDL ulcerative colitis agents and to cover for OHP above the line diagnoses only.

Methods: A Medline literature search ending August 2012 for new systematic reviews and randomized controlled trials (RCT's) comparing aminosalicylates in patients with ulcerative colitis (UC) was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Institute for Clinical and Economic Review (ICER), Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class review. Randomized controlled trials (RCTs) will be emphasized only if evidence is lacking or insufficient from those preferred sources. The literature search for RCT's was done from September 2010 to current and limits placed were humans, English, and all clinical trials.

New Trials: A literature search for RCTs using the above criteria and limits resulted in 28 citations. After reviewing the inclusion criteria, 6 potentially clinically relevant trials resulted (Appendix 1). Trials were excluded mainly because of irrelevant comparisons, duplicate trials, and lack of UC indication. The following table describes these trials; a quality assessment was not performed.

Table 1: Potentially relevant clinical trials

Study	Comparison	Population	Primary Outcome	Results
Ito H, et al. MC, RCT, DB, PC [1]	Asacol 2.4g/day, Asacol 3.6 g/day vs. Pentasa 2.25 g/day vs.	Japanese nationality with mild-moderate UC N=229	A decrease in the UC disease activity index (UC-DAI)	UC-DAI Score Decrease patients enrolled and followed-up in 21 month period (improvement defined as patients with decrease by 2 points or more)

	Placebo			ASA-2.4 g: 1.5 ASA-3.6 g: 2.9 PEN-2.25 g: 1.3 Placebo: 0.3 ASA 3.6g vs PEN 2.25g: difference of 1.6 (95% CI: 0.6, 2.6); p=0.003 ASA2.4 g vs PEN2.25g: 0.2 (95% CI:-0.8, 1.2; no p-value reported
Ito H, et al. MC, RCT, DB, DC[2]	Mesalamine Asacol -2.4g/day vs. Pentasa - 2.25g/day	Japanese nationality with mild-moderate UC N=131	Proportion of patients without bloody stools	<u>Proportion of patients without bloody stools at the end of 12 months</u> ASA2.4g: 76.9% PEN2.25g: 69.2% Difference: 7.7% (95% CI:-7.4, 22.8)
Sandborn W, et al. MC, RCT, DB, DC[3]	Mesalamine 1.6-2.4g/day QD vs. BID	Patients with mild-moderate UC currently in clinical remission N=1023	Maintenance of clinical remission at month 6	<u>Clinical remission maintenance at month 6</u> QD: 90.5% remission BID: 91.8% remission Difference of 1.3;BID-QD 95% CI: -2.3, 4.9 p-value=0.50
Lichtenstein G, et al. RCT, DB, PC[4]	Mesalamine Granules (MG) Apriso 1.5 gram vs. placebo QD	Patients with UC in remission N=305	Percentage of patients who remained relapse-free at month 6/end of treatment	<u>Percentage of patients who remained relapse-free at month 6/end of treatment</u> MG: 78.9% P: 58.3% P<0.001
Kruis W, et al. MC, RCT, DB, DD, DC[5]	Mesalamine oral granules3.0g QD, 1.5g QD, 0.5g TID	Endoscopically and histologically confirmed ulcerative colitis in remission N=648	Proportion of patients still in clinical remission at the final visit	<u>Proportion of patients still in clinical remission at 52 weeks (ITT population)</u> 3.0g: 75% 1.5g: 61% 0.5g: 69% For all three doses, =0.024; 95% CI: -0.026, 0.143 3.0g vs.1.5g p<0.001; 95% CI: 0.050, 0.225

RCT = randomized controlled trial, PC = placebo controlled, DB = double blind; DD= double-dummy MC=multicenter; DC=direct comparison; SB=single blind

New drugs:
None

New Formulations/Dosage Forms:
None

New FDA Indications:

- Mesalamine MMX Tablets (Lialda®) was updated to include induction and maintenance of remission of ulcerative colitis-July 2011[6]
    - The recommended dosage for the induction of remission in adult patients with active, mild to moderate ulcerative colitis is two to four 1.2 g tablets taken once daily with a meal for a total daily dose of 2.4 g or 4.8 g. The recommended dosage for the maintenance of remission is two 1.2 g tablets taken once daily with a meal for a total daily dose of 2.4 g. [6]
- Mesalamine Capsules (Pentasa) was updated to include maintenance of remission of ulcerative colitis

New FDA safety alerts:[7]
No unlabeled or unexpected serious adverse events were identified for Asacol HD (mesalamine) after a postmarketing drug safety evaluation was completed from January 2011 through June 2011.

New Systematic Reviews:
Three systematic reviews and meta-analyses from the American Journal of Gastroenterology were identified (Appendix 2). [8],[9],[10] These reviews met the PRISMA criteria for good quality reviews, but lacked individual RCT risk of bias assessment; and therefore data should be interpreted with caution. One evaluated the general efficacy of 5-aminosalicylates (5-ASA) in UC; another looked at the efficacy of oral vs. topical 5-ASA or combined therapy in UC; and the third compared once daily dosing versus conventional therapy of mesalamine in UC. These reviews concluded that combined therapy of topical and oral 5-ASA was superior to oral therapy for induction of remission in mild to moderate UC (RR of no remission = 0.65; 95 % CI = 0.47 – 0.91; number needed-to-treat (NNT) = 5), and doses greater than 2.0 grams/day of 5-ASA therapy were more effective for inducing remission and preventing relapse (RR = 0.91; 95 % CI 0.85 – 0.98). In addition, once daily dosing of mesalamine was as effective as conventional scheduled dosing for prevention of relapse of quiescent UC (RR of relapse = 0.94; 95 % CI: 0.82 – 1.08), but data on compliance with once daily dosing is lacking.

In the Efficacy of 5-ASA in UC systematic review (SR) [8], there were 37 trials in total, (19 reviewing 5-ASA therapy in active UC and 18 reviewing 5-ASA therapy in quiescent UC). Many of the individual trials in this study lacked randomization and details on allocation concealment, but only a couple were unclear about the blinding process. Of these trials, 11 (n=2086; two considered low risk of bias) looked at 5-ASA versus placebo in inducing remission in active UC, finding there was no statistical significance between the 5-ASA agents, but the data favored 5-ASA over placebo (NNT=6). Ten trials (n=2414) compared high dose mesalamine therapy versus standard dosing in inducing remission in active UC, with the data favoring the higher doses (>2 grams/day). There were no differences in adverse events between the high dose verses the standard dose. Eight trials (n=1015; one trial with low risk of bias) favored the high or standard dose of 5-ASA versus low dose in inducing remission in active UC. Eleven trials (n=1502; two with low risk of bias) favored 5-ASA therapy versus placebo in relapsing quiescent UC (NNT=4). Seven trials (n=1534) favored 5-ASA high dose or standard dose therapy over low dose in preventing relapsing quiescent UC.

In the Once Daily Dosing vs. Conventional Dosing SR[9], seven trials in total (n=2745) compared once-daily dosing (n=1349) of mesalamine with a conventional dosing schedule (n=1396) to an identical total daily dose of mesalamine. Many of these trials were unclear about the randomization and concealment procedure, and the majority of the studies were single-blinded. Two of the trials were at a low risk for bias, and the majority of the trials evaluated mesalamine use in preventing relapse in quiescent UC. Five trials compared once-daily therapy to twice daily and two trials compared it to three times daily. In total 423 (31.4%) of the patients taking once daily mesalamine relapsed compared to 461 (33.0%) using conventional therapy (RR 0.94; 95% CI: 0.82-1.08), demonstrating no statistically significant difference between them. Five studies provided extractable adverse event data, but no statistically significant differences were noted between the once-daily dosing and conventional therapy.

Twelve trials met inclusion criteria in the Efficacy of Oral vs. Topical, or Combined Oral and Topical 5-Aminosalicylates in UC review[10], comparing a mix of topical versus oral mesalamine and sulfasalazine therapy versus combined topical and oral therapy. The majority of the RCTs lacked randomization and concealment data and a few were single blinded and unblended. Four trials (n=214) compared topical versus oral therapy in inducing remission in active UC. Overall, there was no statistically significant difference in failure to achieve remission with topical 5-ASA compared to oral therapy, with 52 (49.5%) of 105 patients receiving topical 5-ASA therapy failing to achieve remission, compared to 64 (58.7%) of 109 patients receiving oral therapy (RR 0.82; 95% CI: 0.52-1.28). Four trials (n=322) compared combined topical and oral therapy with oral therapy in inducing remission in active UC with one trial at low risk of bias. The NNT with combined 5-ASA therapy in one patient failing to achieve remission was 5, with the results favoring the combined therapy (95% CI: 3-13). Topical 5-ASA therapy versus oral in preventing relapse in quiescent UC was compared in three trials (n=129), with the data favoring intermittent topical therapy over oral therapy (NNT=4). Combined oral and topical therapy versus oral 5-ASA therapy in preventing relapse in quiescent UC (n=96) resulted in a RR of relapse of 0.48 (95% CI: 0.17-1.38). One of these trials was unblinded and stopped early due to concern of relapse rates being higher in the oral therapy group.

Guidelines:
Guidelines from the American College of Gastroenterology in 2010 recommend the following:
-Induction of remission-mild to moderate distal colitis:

- Either oral aminosalicylates or topical mesalamine
- Topical mesalamine agents are considered superior to oral aminosalicylates
- The combination of oral and topical aminosalicylates is more effective than either alone
- In patients refractory to oral aminosalicylates, mesalamine enemas or suppositories may still be effective

-Induction of remission-mild to moderate extensive colitis:

- Begin therapy with oral sulfasalazine in daily doses titrated up to 4 – 6 g per day, or an alternate aminosalicylate in doses up to 4.8 g per day of the active 5-aminosalicylate acid (5-ASA) moiety

-Maintenance of remission in distal colitis:

- Mesalamine suppositories are effective in patients with proctitis
- Mesalamine enemas are effective in patients with distal colitis when dosed even as infrequently as every third night
- Sulfasalazine, mesalamine compounds, and balsalazide are also effective in maintaining remission
- The combination of oral and topical mesalamine is more effective than either one alone for remission maintenance

-Maintenance of remission in extensive colitis:

- Sulfasalazine, olsalazine, mesalamine, and balsalazide are all effective in reducing relapses

Recommendations:

- Accept scan as is; no further research or review needed at this time. Evaluate comparative costs of agents in executive session.
- Continue to include at least one drug in each formulation as preferred on the PDL.

References:

1. Ito H, Iida M, Matsumoto T, et al. Direct comparison of two different mesalamine formulations for the induction of remission in patients with ulcerative colitis: a double-blind, randomized study. *Inflammatory Bowel Diseases*. 2010;16(9):1567–74.

2. Ito H, Iida M, Matsumoto T, et al. Direct comparison of two different mesalamine formulations for the maintenance of remission in patients with ulcerative colitis: a double-blind, randomized study. *Inflammatory Bowel Diseases*. 2010;16(9):1575–82.

3. Sandborn W, Korzenik J, Lashner B, et al. Once-daily dosing of delayed-release oral mesalamine (400-mg tablet) is as effective as twice-daily dosing for maintenance of remission of ulcerative colitis. *Gastroenterology*. 2010;138(4):1286–96.

4. Lichtenstein G, Gordon G, Zakko S, et al. Clinical trial: once-daily mesalamine granules for maintenance of remission of ulcerative colitis - a 6-month placebo-controlled trial. *Alimentary Pharmacology & Therapeutics*. 2010;32(8):990–9.

5. Kruis W, Jonaitis L, Pokrotnieks J, et al. Randomised clinical trial: a comparative dose-finding study of three arms of dual release mesalazine for maintaining remission in ulcerative colitis. *Alimentary Pharmacology & Therapeutics*. 2011;33(3):313–22.

6. Anonymous. Drugs@FDA. *Label and Approval History: Lialda*. 2011.

7. Research C for DE and. Surveillance - Postmarketing Drug Safety Evaluation Summaries Completed from January 2011 through June 2011.
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm296188.htm

8. Ford A, Achkar J, Khan K, et al. Efficacy of 5-aminosalicylates in ulcerative colitis: systematic review and meta-analysis. *Journal of Gastroenterology*. 2011;106(4):601–16.

9. Ford A, Khan K, Sandborn W, Kane S, Moayyedi P. Once-daily dosing vs. conventional dosing schedule of mesalamine and relapse of quiescent ulcerative colitis: systematic review and meta-analysis. *Journal of Gastroenterology*. 2011;106(12):2070–7.

10. Ford A, Khan K, Achkar J, Moayyedi P. Efficacy of oral vs. topical, or combined oral and topical 5-aminosalicylates, in Ulcerative Colitis: systematic review and meta-analysis. *Journal of Gastroenterology*. 2012;107(2):167–76.

Appendix 1: Abstracts of new randomized controlled trials.

1. Ito H, Iida M, Matsumoto T, et al. Direct comparison of two different mesalamine formulations for the induction of remission in patients with ulcerative colitis: a double-blind, randomized study. *Inflammatory Bowel Diseases*. 2010;16(9):1567–74.

BACKGROUND: Mesalamine is the first-line drug for the treatment of ulcerative colitis (UC). We directly compared the efficacy and safety of two mesalamine formulations for the induction of remission in patients with UC.
METHODS: In a multicenter, double-blind, randomized study, 229 patients with mild-to-moderate active UC were assigned to 4 groups: 66 and 65 received a pH-dependent release formulation of 2.4 g/day (pH-2.4 g) or 3.6 g/day (pH-3.6 g), respectively; 65 received a time-dependent release formulation of 2.25 g/day (Time-2.25 g), and 33 received placebo (Placebo). The drugs were administered three times daily for eight weeks. The primary endpoint was a decrease in the UC disease activity index (UC-DAI).
RESULTS: In the full analysis set (n = 225) the decrease in UC-DAI in each group was 1.5 in pH-2.4 g, 2.9 in pH-3.6 g, 1.3 in Time-2.25 g and 0.3 in Placebo, respectively. These results demonstrate the superiority of pH-3.6 g over Time-2.25 g (P = 0.003) and the noninferiority of pH-2.4 g to Time-2.25 g. Among the patients with proctitis-type UC, a significant decrease in UC-DAI was observed in pH-2.4 g and pH-3.6 g as compared to Placebo, but not in Time-2.25 g. No differences were observed in the safety profiles.
CONCLUSIONS: Higher dose of the pH-dependent release formulation was more effective for induction of remission in patients with mild-to-moderate active UC. Additionally, the pH-dependent release formulation was preferable to the time-dependent release formulation for patients with proctitis-type UC

2. Ito H, Iida M, Matsumoto T, et al. Direct comparison of two different mesalamine formulations for the maintenance of remission in patients with ulcerative colitis: a double-blind, randomized study. *Inflammatory Bowel Diseases*. 2010;16(9):1575–82.

BACKGROUND: Mesalamine has been used as the first-line medication for the treatment of ulcerative colitis (UC). We directly compared the efficacy and safety of two different mesalamine formulations in the maintenance of remission in patients with UC.
METHODS: In a multicenter, double-blind, randomized study, 131 patients with quiescent UC were assigned to two groups: 65 to receive a pH-dependent release formulation of mesalamine at 2.4 g/day (pH-2.4 g) and 66 to receive a time-dependent release formulation of mesalamine at 2.25 g/day (Time-2.25 g). Both formulations were administered three times daily for 48 weeks. The primary endpoint was the proportion of patients without bloody stools.
RESULTS: In the full analysis set (n = 130), the proportion of patients without bloody stools was 76.9% in the pH-2.4 g and 69.2% in the Time-2.25 g, demonstrating the noninferiority of pH-2.4 g to Time-2.25 g. No statistically significant difference in time to bloody stools was found between the two formulations (P = 0.27, log-rank test), but the time to bloody stools tended to be longer in pH-2.4 g compared to Time-2.25 g, and a similar trend was observed with regard to the time to relapse. No differences were observed between the safety profiles of the two formulations.
CONCLUSIONS: The pH- and time-dependent releases of mesalamine formulations were similarly safe and effective. Interestingly, the remission phase tended to be longer in the group that received the pH-dependent formulation compared to the group that received the time-dependent formulation.

3. Sandborn W, Korzenik J, Lashner B, et al. Once-daily dosing of delayed-release oral mesalamine (400-mg tablet) is as effective as twice-daily dosing for maintenance of remission of ulcerative colitis. *Gastroenterology*. 2010;138(4):1286–96.

BACKGROUND & AIMS: The practice of dosing mesalamines in divided doses for the treatment of ulcerative colitis (UC) began with sulfasalazine and was driven by sulfapyridine toxicity. This convention and the assumption that dosing multiple times a day is necessary to treat UC had not been challenged until recently. This study was conducted to determine the efficacy and safety of once-daily dosing of delayed-release mesalamine (Asacol 400-mg tablets) compared

with twice-daily dosing for maintaining remission in UC patients.
METHODS: A multicenter, randomized, investigator-blinded, 12-month, active-control trial was conducted to assess the noninferiority of delayed-release mesalamine 1.6-2.4 g/day administered once daily compared with twice daily in patients with mild-to-moderate UC currently in clinical remission. The primary end point was maintenance of clinical remission at month 6.
RESULTS: A total of 1023 patients were randomized and dosed. The primary objective of noninferiority was met. At month 6, 90.5% of patients receiving once-daily dosing had maintained clinical remission, compared with 91.8% of patients receiving twice-daily dosing (95% confidence interval for twice daily - once daily, -2.3 to 4.9). At month 12, 85.4% of patients receiving once-daily dosing had maintained clinical remission, compared with 85.4% of patients receiving twice-daily dosing (95% confidence interval for twice daily - once daily, -4.6 to 4.7). Both regimens had low rates of withdrawals as a result of adverse events and serious adverse events.
CONCLUSIONS: Once-daily dosing of delayed-release mesalamine at doses of 1.6-2.4 g/day was shown to be as effective as twice-daily dosing for maintenance of clinical remission in patients with UC.

4. Lichtenstein G, Gordon G, Zakko S, et al. Clinical trial: once-daily mesalamine granules for maintenance of remission of ulcerative colitis - a 6-month placebo-controlled trial. *Alimentary Pharmacology & Therapeutics*. 2010;32(8):990–9.

BACKGROUND: Ulcerative colitis (UC) is a chronic relapsing and remitting idiopathic inflammatory bowel disorder.
AIM: To evaluate once-daily mesalamine (mesalazine) granules (MG) for maintenance of remission of UC.
METHODS: Randomized, double-blind, placebo-controlled trial of patients (n=209 MG, n=96 placebo) with UC in remission [revised Sutherland Disease Activity Index (SDAI) rectal bleeding=0, mucosal appearance <2] who took MG 1.5 g or placebo once-daily for up to 6 months. Primary efficacy endpoint: the percentage of patients who remained relapse-free at month 6/end of treatment. Relapse was defined as SDAI rectal bleeding score >=1 and a mucosal appearance score >=2, a UC flare, or initiation of medication to treat a UC flare.
RESULTS: The percentage of relapse-free patients at month 6/end of treatment was higher with MG than placebo (78.9% vs. 58.3%, P < 0.001) in the intent-to-treat analysis. Significant differences (P <= 0.025) favouring MG were observed for most secondary endpoints including improvement in rectal bleeding, physician's disease activity rating, stool frequency, the SDAI at month 6/end of treatment, patients classified as a treatment success and relapse-free duration. The incidence of adverse events was similar between groups.
CONCLUSIONS: Once-daily mesalamine (mesalazine) was effective in maintaining remission of UC for 6 months.

5. Kruis W, Jonaitis L, Pokrotnieks J, et al. Randomised clinical trial: a comparative dose-finding study of three arms of dual release mesalazine for maintaining remission in ulcerative colitis. *Alimentary Pharmacology & Therapeutics*. 2011;33(3):313–22.

BACKGROUND: Comparative data regarding different regimens of oral mesalazine (mesalamine) for maintaining remission in ulcerative colitis are limited.
AIM: To evaluate whether 3.0 g mesalazine once-daily (OD) is superior to the standard treatment of 0.5 g mesalazine three times daily (t.d.s.) and to prove the therapeutic equivalence of OD vs. t.d.s. dosing of total 1.5 g mesalazine for remission maintenance in patients with ulcerative colitis.
METHODS: A 1-year, multicentre, double-blind, double-dummy study was undertaken in patients with endoscopically and histologically confirmed ulcerative colitis in remission. Patients were randomised to oral mesalazine 3.0 g OD, 1.5 g OD or 0.5 g t.d.s. The primary efficacy endpoint was the proportion of patients still in clinical remission at the final visit, with clinical relapse being defined as CAI score >4 and an increase of >=3 from baseline.
RESULTS: The primary efficacy endpoint occurred in 162/217 3.0 g OD patients (75%), 129/212 1.5 g OD patients (61%) and 150/218 0.5 g t.d.s. patients (69%) in the intention-to-treat population, and in 152/177 (86%), 121/182 (67%) and 144/185 (78%) in the per protocol population respectively; 3.0 g OD was superior to both low-dose regimens for the primary endpoint (i.e. P < 0.001, 3.0 g OD vs. 1.5 g OD; P = 0.024, 3.0 g OD vs. 0.5 g t.d.s.; superiority test, per protocol population). Safety analysis, including comprehensive renal monitoring, revealed no concern in any treatment group.

CONCLUSION: Mesalazine 3.0 g once daily was the most effective dose for maintenance of remission in ulcerative colitis of the three regimens assessed, with no penalty in terms of safety.

Appendix 2: Abstracts of Systematic Reviews

8. Ford A, Achkar J, Khan K, et al. Efficacy of 5-aminosalicylates in ulcerative colitis: systematic review and meta-analysis. *Journal of Gastroenterology*. 2011;106(4):601–16.

OBJECTIVES: The efficacy of 5-aminosalicylic acids (5-ASAs) in ulcerative colitis (UC) has been studied previously in meta-analyses. However, several randomized controlled trials (RCTs) have been published recently, and no previous meta-analysis has studied the effect of 5-ASA dosage used.

METHODS: MEDLINE, EMBASE, and the Cochrane central register of controlled trials were searched (through

December 2010). Eligible trials recruited adults with active or quiescent UC, comparing different doses of 5-ASAs with themselves or placebo. Dichotomous data were pooled to obtain relative risk (RR) of failure to achieve remission in active UC, and RR of relapse of disease activity in quiescent UC, with a 95 % confidence interval (CI). The number needed to treat (NNT) was calculated from the reciprocal of the risk difference.

RESULTS: The search identified 3,061 citations, and 37 RCTs were eligible. Of these, 11 compared 5-ASA with placebo in active UC remission, with the RR of no remission with 5-ASAs of 0.79 (95 % CI 0.73 –

0.85; NNT = 6). Doses of ≥ 2.0 g / day were more effective than < 2.0 g / day for remission (RR = 0.91; 95 % CI 0.85 – 0.98). There were 11 RCTs comparing 5-ASAs with placebo in preventing relapse of quiescent UC, with the RR of relapse of 0.65 (95 % CI 0.55 – 0.76; NNT = 4). Doses of ≥ 2.0 g / day appeared more effective than < 2.0 g / day for preventing relapse (RR = 0.79; 95 % CI 0.64 – 0.97).

CONCLUSIONS: 5-ASAs are highly effective for inducing remission and preventing relapse in UC. Evidence suggests that doses of ≥ 2.0 g / day have greater efficacy, although doses > 2.5 g / day do not appear to lead to higher remission rates.

9. Ford A, Khan K, Sandborn W, Kane S, Moayyedi P. Once-daily dosing vs. conventional dosing schedule of mesalamine and relapse of quiescent ulcerative colitis: systematic review and meta-analysis. *Journal of Gastroenterology*. 2011;106(12):2070–7.

OBJECTIVES: Maintenance therapy with 5-aminosalicylates (5-ASAs) is recommended in patients with quiescent ulcerative colitis (UC), but compliance rates are low. Once-daily dosing may improve adherence, but impact on the relapse of disease activity is unclear as no previous meta-analysis has studied this issue.

METHODS: MEDLINE, EMBASE, and the Cochrane central register of controlled trials were searched (through

April 2011). Eligible randomized controlled trials (RCTs) recruited adults with quiescent UC, and compared once-daily dosing of 5-ASAs with a more frequent dosing schedule of an identical total daily dose of the same 5-ASA drug. Minimum treatment duration was 6 months. Trials reported a dichotomous assessment of relapse of disease activity at last point of follow-up. Data concerning noncompliance and adverse events were extracted, where reported. Effect of once-daily vs. more frequent dosing schedule was reported as relative risk (RR) of relapse with a 95 % confidence interval (CI).

RESULTS: The search identified 3,061 citations, and seven RCTs containing 2,745 patients were eligible.

All RCTs used mesalamine. Relapse rates were not significantly different between once-daily and conventional dosing schedules for mesalamine (RR of relapse = 0.94; 95 % CI: 0.82 – 1.08). Noncompliance

(RR = 0.87; 95 % CI: 0.46 – 1.66) and adverse events were no more likely with once-daily dosing (RR = 1.08; 95 % CI: 0.97 – 1.20).

CONCLUSIONS: Once-daily dosing with mesalamine is as effective as conventional dosing schedules for the prevention of relapse of quiescent UC, although there is no definitive evidence that compliance with once daily dosing is better. Adverse events occur at a similar frequency.

10. Ford A, Khan K, Achkar J, Moayyedi P. Efficacy of oral vs. topical, or combined oral and topical 5-aminosalicylates, in Ulcerative Colitis: systematic review and meta-analysis. *Journal of Gastroenterology*. 2012;107(2):167–76.

OBJECTIVES: Efficacy of 5-aminosalicylic acids (5-ASAs) in ulcerative colitis (UC) has been studied previously in meta-analyses. However, no recent meta-analysis has studied the relative efficacies of differing routes of administration.

METHODS: MEDLINE, EMBASE, and the Cochrane central register of controlled trials were searched (through May 2011). Eligible trials recruited adults with mildly to moderately active UC, or quiescent UC, and compared oral 5-ASAs with either topical 5-ASAs or a combination of oral and topical 5-ASAs. Dichotomous data were pooled to obtain relative risk (RR) of failure to achieve remission in active UC, and RR of relapse of disease activity in quiescent UC, with a 95 % confidence interval (CI).The number needed to treat (NNT) was calculated from the reciprocal of the risk difference.

RESULTS: The search identified 3,061 citations, and 12 randomized controlled trials (RCTs) were eligible. Four compared topical with oral 5-ASAs in active UC remission, with an RR of no remission with topical 5-ASAs of 0.82 (95 % CI = 0.52 – 1.28). Four trials compared combined with oral 5-ASAs in active UC (RR of no remission = 0.65; 95 % CI = 0.47 – 0.91; NNT = 5). Three RCTs compared intermittent topical with oral 5-ASAs in preventing relapse of quiescent UC (RR = 0.64; 95 % CI = 0.43 – 0.95; NNT = 4), and two compared combined with oral 5-ASAs (RR of relapse = 0.48; 95 % CI = 0.17 – 1.38).

CONCLUSIONS: Combined 5-ASA therapy appeared superior to oral 5-ASAs for induction of remission of mildly to moderately active UC. Intermittent topical 5-ASAs appeared superior to oral 5-ASAs for preventing relapse of quiescent UC.