Supplementary Material

Figure 1: Prisma Flow Diagram

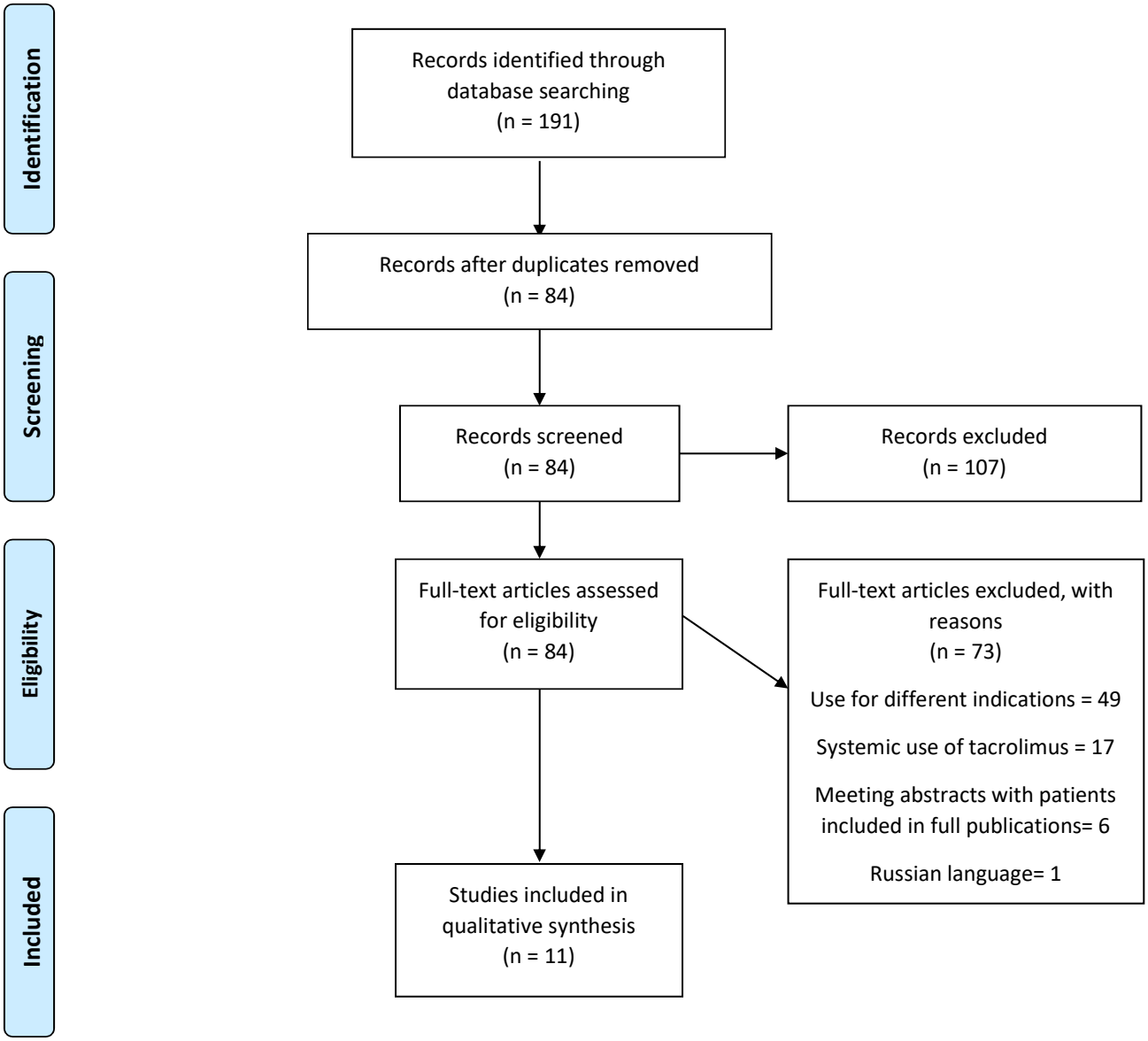

Table 1

Author and Year	Study Design	No. of Patients	Disease Extent	Previous Treatment	Intervention	Treatment Duration	Trough level µg/L	Response	Remission	Safety
Proctitis										
Lawrance *et al*, 2008 [37]	Prospective	8	E1=4, E2=2, E3=2 *(1=IRA). (Maximal active inflammation 15-30cm)	Oral/rectal 5-ASA, rectal steroids, oral steroids, AZA, 6MP, IFX, Abatacept	Tacrolimus ointment (dose range: total of 1.8mg - 6mg per day)	8 weeks	Range: Undetectable – 6.9 ng/mL	6/8 (75%) - based on mMS[1](reduction of ≥3 points, rectal bleeding score 0-1)	6/8 (75%) – based on mMS of 2 or less, no subscore >1	Rectal burning (1/8). Subsided with dose reduction and achieved remission at week 8.
van Dieren *et al*, 2009 [38]	Prospective	12	Proctitis	Local steroids either alone or in combination with local 5-aminosalicylate acid (5-ASA) treatment for at least 4 weeks	Tacrolimus suppositories. Dose: 2mg	4 weeks	Range: Undetectable – 1.7 ng/mL	10/12 (83%) had improvement of disease activity based on Mayo Score	8/12 (67%) showed endoscopic improvement (Mayo)	No reported physical exam abnormalities, new disorders, or abnormal lab values.
Lawrance *et al*, 2017 [39]	RCT Tacrolimus vs placebo	21 Tacolimus:11 Placebo:10	Up to 25cm from anal verge	5-ASA oral/topical, steroid oral/topical, MTX, AZA	Tacrolimus ointment. Dose: 0.5 mg/mL, 3 mL twice a day	8 weeks	Range: Undetectable – 32.2 ng/mL	(8/11 vs 1/10) 73% vs 10%; *P* = .004 (reduction in the Mayo Score of ≥3 points)	(5/11 vs 0/10) 45% vs 0%; *P* = .015 (Mayo Score ≤2, no subscore >1). Mucosal healing: (8/1) 73% vs 10%; P = .004	(1) URTI (resolved spontaneously), (1) tremor (trough undetectable), (1) self-limiting dizziness, (1) headache (resolved with paracetamol).
Jaeger *et al*, 2018 [40]	Retrospective	43	Up to 25cm from anal verge	oral/rectal 5-ASA, rectal steroids, oral steroids, AZA, 6MP, IFX	Tacrolimus suppositories. Dose: 2mg twice a day	Median duration of treatment was 76 days (from baseline to	Mean tacrolimus level: 5.5 ± 3.9 ng/mL	NA[2]	Colitis Activity Index ≤4: 26/43 (60%)	(1) Creatinine increased to 1.5 mg/dl - normalized after stopping therapy,

[1] Modified Mayo Score
[2] Not Available/not reported

						the last documented visit)				(4) hand tremors, (3) headaches, (1) fatigue
Lie *et al*, 2019 [41]	RCT Tacrolimus vs beclomethasone	85 Tacrolimus: 43 Beclomethasone: 42	Up to 20cm from anal verge	Mesalamine-refractory proctitis, or recurring proctitis	Tacrolimus suppository 2mg daily, or beclomethasone suppository 3 mg once daily	4 weeks	Mean tacrolimus level was 2.7 ± 2.8 ng/mL (range: 0–12.8) at Week 4	Clinical response (reduction in the Mayo Score of ≥3 points) Tacrolimus: 22/35 (62.9%), Beclomethasone.:22/37 (59.5%). P=0.812.	Clinical remission (Mayo Score ≤2, no subscore >1): Tacro: 16/35 (45.7%), Becl.: 15/39 (38.5%). P=0.638. Endoscopic remission: Tacro 11/37 (29.7%), Becl.: 5/40 (12.5%) P=0.092	Tacrolimus: 29 events (21 patients) = 48.8%, Beclomethasone: 18 events (14 patients) =33.3%. P=0.188
Fehily *et al*, 2019 [42]	Retrospective	17 patients (12/5: UC/CD) severe refractory proctitis. Four patients with inflammatory strictures.	NA	All patients had failed immunosuppressive therapy, most had failed both a thiopurine (88%) and biologic therapy (71%)	Tacrolimus enemas. Dose: 1–4 mg, according to tolerance, followed by 1–3 mg three times weekly maintenance	Median duration: 20 weeks (3-204)	NA[2]	16/17 (94%) clinical and biochemical improvement. 13/17 (79%) endoscopic improvement	Endoscopic remission: 10/17 (58.82%). In all four patients with strictures, the inflammation resolved and the stricture became endoscopically passable without dilatation.	3/17 (18%) - disease flare.
Smith *et al*, 2019 [43]	Retrospective	21 (20 UC, 1 CD)	Proctitis	5-ASA topical/Oral, steroid topical, MTX, AZA, biologics	Tacrolimus suppository. Dose: 2mg twice a day	4 weeks	NA[2]	16/21 (76.1%) - clinical response (PRO2 decrease by >2 points)	13/21 (62%) - clinical remission (PRO2 = 0)	None

Table 2

Author and Year	Study Design	No. of Patients	Disease Extent	Previous Treatment	Intervention	Treatment Duration	Trough level µg/L	Response	Remission	Safety
Crohn's disease with perianal manifestations (fissuring, fistulizing)										
Casson *et al*, 2000[44]	Prospective	6 (pediatrics)	2/6: highly destructive perianal disease, 3/6: perianal ulcers, 1/6: perianal fistula	Steroids (oral/topical) 6/6, topical cyclosporine 3/6, AZA 3/6	Tacrolimus ointment. Dose: 0.5mg/g twice a day.	4 weeks – 6 months	Undetectable	NA[2]	5/6 (83.3%) clinical remission (2 highly destructive perianal disease, 2 perianal ulcer, 1 perianal fistula). 1/6 (16.7%) no effect	None
Hart *et al*, 2006[45]	RCT Tacrolimus vs placeb[3]o	19 Tacrolimus: 10 Placebo: 9	Fistulizing disease: 12 (6 on active treatment and 6 on placebo) Ulcerating disease: 7 (4 on active treatment and 3 on placebo)	Local steroids either alone or in combination with local 5-aminosalicylate acid (5-ASA) treatment, Thiopurines, Infliximab	Tacrolimus ointment. Dose: 1 mg/g (0.1%) twice a day. (Ointment was applied around the external opening of fistulas and to any associated inflamed or indurated skin. For those with ulceration, ointment was applied to inflamed and indurated areas, both perianally and intra-anally.)	12 weeks	Range: Undetectable – 4.2 ng/mL	Fistula: 1/6 (16.67%) complete response, 2/6 (33.33%) global improvement (clinical improvement) vs placebo. (1/6 partial response, 2/6 global improvement - all of them had setons in place). Ulceration: 3/4 (75%) global improvement (clinical),	Fistula: 1/6 (16.67%) complete response on tacrolimus vs 0/6 with placebo. Ulcers: 0/4 vs 0/3.	Skin irritation (1), abscess (2), Temporary reduction in kidney function W8 and normalized at W12 without intervention (1) (continued tacrolimus till W12)

[2] Not Available/not reported

								none achieved complete healing vs placebo. 0/3 had any improvement.		
Niyogi *et al*, 2010[46]	Retrospective	7 (pediatrics)	Fistula-in-ano	Amoxicillin – clavulanic acid	Tacrolimus ointment. Dose: 0.03% twice a day	12 weeks	NA[2]	NA[2]	6/7 (85.71%) - remission (defined as no active inflammation on magnetic resonance imaging, patient is asymptomatic)	NA[2]

Table 3

Author and Year	Study Design	No. of Patients	Disease Extent	Previous Treatment	Intervention	Treatment Duration	Trough level µg/L	Response	Remission	Safety
Chronic Antibiotic-Refractory Pouchitis										
Uchino *et al*, 2013[47]	Prospective	10	Chronic antibiotics-refractory pouchitis. PDAI ≥ 7	Ciprofloxacin, metronidazole, topical 5-ASA	Tacrolimus enema. Dose: 0.08mg/kg = 4-5mg/day. Once daily (AM)	8 weeks	Range: 1.2-8.2 ng/mL at week 8	9/10 (90%) pouchitis clinical sub-score decrease of more than three points.	7/10 (70%) pouchitis clinical sub-score of zero PDAI score decreased from 15.9 +/- 0.8 to 7.8 +/- 0.8 ($p < 0.01$)	3/10 (30%) Mild burning in the pouch; did not lead to discontinuation

Supplementary Material

Assessing risk of bias in included studies using Higgins Scale [36]

Study ID	Study design	Sampling design	Patients enrolled consecutively	Adequate sequence generation	Allocation concealment	Blinding	Free of selective reporting	Selection bias
Lawrance, et al. 2008 [37]	Pilot study	Prospective	Yes	Not used	Not used	Not reported	Yes	Moderate
van Dieren, et al. 2009 [38]	Clinical trial (phase1)	Prospective	Not reported	Not used	Not used	Not reported	Yes	Moderate
Lawrance, et al. 2017 [39]	RCT	Prospective	Not reported	Yes	Yes	Yes	Yes	Low
Jaeger, et al. 2018 [40]	Experimental trial	Retrospective	Yes	Not used	Not used	Not used	Yes	Moderate
Lie, et al. 2018 [41]	RCT	Prospective	Not reported	Yes	Yes	Yes	Yes	Low
Fehily, et al. 2019 [42]	Experimental trial	Retrospective	Yes	Not used	Not used	Not used	Yes	Moderate
Smith, et al. 2019 [43]	Experimental trial	Retrospective	Yes	Not used	Not used	Not used	Yes	Moderate
Casson, et al. 2000 [44]	Experimental trial	Prospective	Yes	Not used	Not used	Not used	Yes	Moderate
Hart, et al. 2007 [45]	RCT	Prospective	Not reported	Unclear	Unclear	Yes	Yes	Moderate
Niyogi, et al. 2009 [46]	Experimental trial	Retrospective	Yes	Not used	Not used	Not used	Yes	Moderate
Uchino, et al. 2013 [47]	Experimental trial	Prospective	Yes	Not used	Not used	Not used	Yes	Moderate