

Efficacy of tacrolimus for induction of remission in patients with moderate-to-severe ulcerative colitis: a systematic review and meta-analysis

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ABSTRACT – Background – There is evidence that shows that calcineurin inhibitors may be useful for the treatment of severe ulcerative colitis. However, evidence regarding the efficacy of tacrolimus for remission induction in this setting is scarce. **Objective** – To develop a systematic review on the existing evidence regarding the clinical efficacy of tacrolimus for the induction of remission in patients with moderate-to-severe ulcerative colitis. **Methods** – A literature search was undertaken from 1966 to August 2016 using MEDLINE, Embase, LILACS and the Cochrane Library. The following MeSH terms were used: “Inflammatory Bowel Diseases” or “Ulcerative Colitis” and “Calcineurin Inhibitors” or “Tacrolimus” or “FK506”. Studies performed in adult ulcerative colitis patients that evaluated the clinical efficacy of tacrolimus for the induction of remission were considered for revision. A meta-analysis was performed with those included studies that were also placebo-controlled and randomized. Clinical response as well as clinical remission and mucosal healing were evaluated. **Results** – Overall, 755 references were identified, from which 22 studies were finally included. Only two of them were randomized, placebo-controlled trials. A total of 172 patients were evaluated. A significantly lower risk of failure in clinical response was found for tacrolimus versus placebo [RR 0.58 (0.45-0.73)]; moreover, a lower risk of failure in the induction of remission was also found versus placebo [RR 0.91 (0.82-1)]. **Conclusion** – Tacrolimus seems to be a valid therapeutic alternative for the induction of remission in patients with moderate-to-severe ulcerative colitis.

HEADINGS – Inflammatory bowel diseases. Tacrolimus. Calcineurin inhibitors.

INTRODUCTION

Inflammatory Bowel Disease (IBD) is an immunological condition that carries a significant morbidity as well as mortality⁽¹⁾. It has been classified as Crohn's Disease (CD) or Ulcerative Colitis (UC). Even though these entities share a common ground, they exhibit differences in terms of clinical presentation and therapeutic alternatives. During the last few years, there has been a significant development of scientific evidence showing the benefit of biological therapy – mainly anti-TNF α agents – in both scenarios⁽⁷⁾.

Nevertheless, approximately 30% of patients with moderate-to-severe disease, whether they are CD or UC patients, do not respond to anti-TNF α therapy (primary failure)⁽³⁾ and a significant proportion of patients (13% to 25% per year of treatment) may develop resistance and hence loss of efficacy to this type of treatment (secondary failure)^(27,33). This is why alternative therapeutic strategies are needed for these patients so that clinical conditions are improved and potentially serious complications can be avoided.

There is some evidence that show the efficacy of calcineurin inhibitors for the treatment of patients with severe UC⁽¹⁸⁾. Due to the effect that these drugs exert on calcineurin, they can inhibit the transcription of the Interleukin-2 gene – among others – which is necessary for the activation of T lymphocytes⁽²⁾. As a consequence, although the quality of the available evidence is far from ideal, cyclosporine has been used in this clinical context; much less evidence is available in the CD scenario.

Bearing this in mind, a class-effect on moderate-to-severe UC could be inferred; consequently, the use of other calcineurin inhibitors such as tacrolimus has been proposed. Tacrolimus has the advantages of oral administration, a well-known safety profile and the previous experience of use in other clinical settings⁽³¹⁾. However, the evidence of the efficacy of its use in moderate-to-severe UC is scarce.

As a consequence, we sought to carry out a systematic review of the available evidence on this matter, with a meta-analysis considering randomized controlled trials.

METHODS

A literature search was carried out from 1966 to August 2016 using the following databases: MEDLINE, Embase, LILACS and The Cochrane Library. The search strategy included the following MeSH terms: “Inflammatory Bowel Disease” or “Ulcerative Colitis” and “Calcineurin Inhibitors” or “Tacrolimus” or “FK-506”. Also, we reviewed the bibliographic references of the papers identified as potentially relevant. Additionally, we manually reviewed the abstracts of the Digestive Disease Week and United European Gastroenterology Week from 2010 to 2016.

The two authors performed bibliographic search in an independent manner. Potentially relevant abstracts were reviewed to check if they fulfilled inclusion criteria. These criteria were: a) studies that addressed the efficacy of tacrolimus in more than five UC patients; b) studies performed in adult population. For meta-

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analysis performance, studies which fulfilled the aforementioned criteria and were randomized controlled trials were included. PRISMA recommendations were followed for this purpose.

Authors' findings were then compared. If there was disagreement regarding the inclusion of a study, this would be discussed until consensus was reached. If data duplication was suspected, the authors of the studies would be contacted to exclude this situation.

The methodological quality of the included studies would be evaluated following the Evidence-Based Gastroenterology Sterring Group recommendations⁽²⁹⁾. In addition, Jadas score was estimated for each study.

Outcome measures were: clinical response, clinical remission after induction treatment and, if available, mucosal healing rate.

Meta-analysis was performed using REVMAN software (Review Manager Version 5.1. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2011). Heterogeneity was estimated by means of I² test and chi square test. If no significant heterogeneity was found, a fixed-effect model would be used for meta-analysis; otherwise, a random-effect model would be preferred. Outcome measures were described as Relative Risks (RR) with their corresponding 95% Confidence Interval (95%CI). Additionally, their corresponding Number Necessary to Treat (NNT) were calculated.

RESULTS

Overall, 755 potentially relevant citations were identified; 48 of them were further chosen for analysis. Figure 1 shows the flow diagram which describes the reasons for citations exclusion. Finally, 22 studies^(4-6,9-17,20-25,28,30,32,33) that fulfilled eligibility criteria were included. Only two studies were randomized controlled trials^(24,25) (Ogata 2006 and Ogata 2012); these were included for meta-analysis.

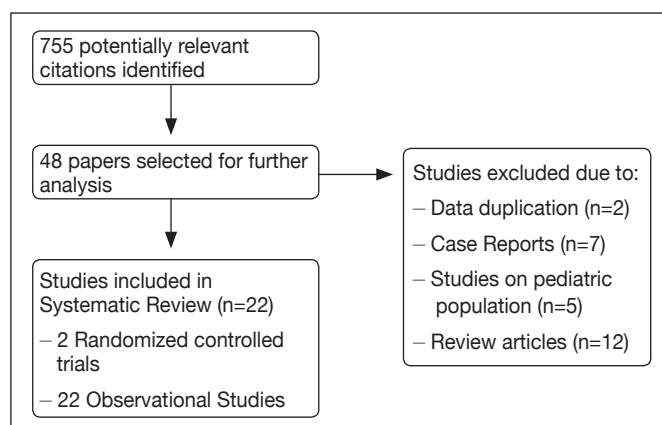


FIGURE 1. Flow-Chart showing the selection process of the studies included in the systematic review.

Table 1 describes the main features of the non-controlled studies that evaluated the efficacy of tacrolimus in patients with UC. The population included in these studies are rather similar – moderate-to-severe UC patients which are steroid-dependent or steroid-refractory– but certain discrepancy was found in the way that clinical response and clinical remission were defined: some studies used Truelove Witts criteria, whereas others used Lichtiger score. Some minor differences in terms of follow up time were also found. It is worth mentioning that only one of these studies⁽¹⁴⁾ (Ikeya 2015) considered mucosal healing as an outcome. The tacrolimus dosage was adjusted to obtain a serum level between 10 to 15 ng/mL. Overall, 609 patients were included in non-controlled studies: in many of these cases, colectomy was delayed but not avoided.

TABLE 1. Characteristics of observational studies included in the systematic review

Author	Year	Country	UC severity and distribution	Remission definition (and time considered)	Number of patients	Interventions	Concomitant treatments	Results
Fellermann ⁽¹⁰⁾	2002	Germany	Moderate-to-severe colitis/steroid-refractory	Truelove-Witts Score. Remission evaluation in 2 weeks. Follow up for 6 months	38	IV Tacrolimus (0.01-0.02 mg/kg/day) or P.O. (0.1-0.2 mg/kg/day)	Antibiotics; aminosalicilates; steroids; thiopurines	28.94% (11/38) = clinical remission in 2 weeks. 16-month colectomy rate= 34%
Hogenauer ⁽¹³⁾	2003	Austria	Moderate-to-severe colitis/steroid-refractory	Truelove Witts Score. Evaluation up to week 12	9	Tacrolimus 0.15 mg/kg/day (adjusted by serum target level: 10-20 ng/mL)	Steroids; thiopurines	66.66% (6/9) = clinical remission in 12 weeks. 3/9= 33.33% of colectomy on follow up
Baumgart ⁽⁴⁾	2006	Germany	Steroid-dependent or refractory (57% pancolitis)	Modified Clinical Activity Index up to 30 days	40	Tacrolimus 0.1 mg/kg/day (adjusted by serum target level: 4-8 ng/mL)	Steroids	45% (18/40) = clinical remission in 30 days; 77.5% (31/40) of clinical response. 22.5% colectomy on follow up
Ng ⁽²²⁾	2007	England	Steroid-dependent moderate-to-severe colitis or previous failure to thiopurines or Infliximab	Truelove Witts score up to 4 weeks	6	Tacrolimus 0.1 mg/kg/day (adjusted by serum target level: 5-10 ng/mL)	Aminosalicilates; steroids; thiopurines; probiotics	50% (3/6)= clinical remission in 4 weeks; 66.66% (4/6) of clinical response
Benson ⁽⁵⁾	2007	USA	Steroid-dependent or refractory moderate-to-severe colitis	Clinical variables and progression to colectomy up to 29 weeks	32	Tacrolimus 0.2 mg/kg/day (adjusted by serum target level:10-12 ng/mL)	aminosalicylates; steroids; thiopurines	9.37% (3/32)= clinical remission; 68.75% (22/32) of clinical response. 37.5% = colectomy on follow up

Continue ➡

Yamamoto ⁽³²⁾	2008	Japan	Moderate-to-severe colitis refractory to other treatments (81.5% pancolitis)	Truelove Witts Score up to 30 days	27	Tacrolimus 0.1 mg/kg/day (adjusted by serum target level:10-15 ng/mL)	aminosalicilates; steroids; thiopurines	70.4% (19/27)= clinical remission in 30 days; 77.8% (21/27) of clinical response. 26.9%= colectomy on follow up
Thin ⁽³⁰⁾	2012	Australia	Moderate-to-severe colitis refractory to other treatments	Colitis Activity Index up to 30 days	24	Tacrolimus 0.1 mg/kg/day (adjusted by serum target level:8-12 ng/mL)	aminosalicilates; steroids	37.5% clinical remission (9/24); 58.3% (14/24) clinical response
Schmidt ⁽²⁸⁾	2013	Germany	Steroid-refractory Moderate-to-severe colitis	Lichtiger score up to 12 weeks; need for colectomy	130	Tacrolimus 0.1 mg/kg/day	aminosalicilates; steroids; thiopurines	72% (94/130) clinical remission; 14% (18/130)= colectomy on follow up
Inoue ⁽¹⁵⁾	2013	Japan	Moderate-to-severe pancolitis without steroid treatment	Lichtiger score. Mayo score for mucosal healing up to 4 weeks.	11	Tacrolimus 0.1 mg/kg/day (adjusted by serum target level:10-15 ng/mL)	aminosalicilates; thiopurines	72.7% (8/11) clinical remission; 100% (11/11) clinical response
Miyoshi ⁽²¹⁾	2013	Japan	Steroid-dependent or refractory moderate-to-severe colitis	Lichtiger score. Mayo score for mucosal healing up to 12 weeks.	51	Tacrolimus initial dose= 5 mg/day; then, oral Tacrolimus (adjusted by serum target level: 10-15 ng/mL)	aminosalicilates; steroids; thiopurines	39.2% (20/51)= clinical remission; 62.74% (32/51)= clinical response
Landy ⁽¹⁷⁾	2013	England	Moderate-to-severe colitis refractory to other treatments	Truelove Witts Score up to 6 months	25	Tacrolimus 0.1 mg/kg/day (adjusted by serum target level:5-10 ng/mL)	aminosalicilates; steroids; thiopurines	20% (5/25)= clinical remission; 24% (6/25)= clinical response
Boschetti ⁽⁶⁾	2014	France	Moderate-to-severe colitis refractory to other treatments	UC-DAI at 4 and 12 weeks	30	Tacrolimus 0.1-0.2 mg/kg/day (adjusted by serum target level:10-15 ng/mL)	steroids; thiopurines	47% (14/30)= clinical remission; 70% (21/30)= clinical response in 4 weeks
Hiraoka ⁽¹¹⁾	2015	Japan	Colitis moderada-severa cortico-dependiente/refractoria	Lichtiger score up to 2-3 weeks	47	Tacrolimus 0.05-0.15 mg/kg/day (adjusted by serum target level: 10-15 ng/mL)	aminosalicilates; steroids; thiopurines	87% (41/47) showed remission and/or clinical response
Ikeya ⁽¹⁴⁾	2015	Japan	Moderate-to-severe colitis	Colitis Activity Index. Mayo score for mucosal healing up to 12 weeks	44	Tacrolimus 0.1 mg/kg/day (adjusted by serum target level:10-15 ng/mL)	aminosalicilates; steroids; thiopurines	86.4% (38/44)= clinical response; 65.9% (29/44)= clinical remission; 43.8% mucosal healing
Kawakami ⁽¹⁶⁾	2015	Japan	Steroid-dependent or refractory moderate-to-severe colitis	Lichtiger score up to 4 weeks	49	Tacrolimus 0.1 mg/kg/day (adjusted by serum target level:10-15 ng/mL)	aminosalicilates; steroids; thiopurines	89.6%= clinical response; 75.6%= clinical remission in 4 weeks
Minami ⁽²⁰⁾	2015	Japan	Moderate-to-severe colitis refractory to other treatments	Mayo score up to 8 weeks	22	Tacrolimus 0.1 mg/kg/day (adjusted by serum target level:10-15 ng/mL)	aminosalicilates; steroids; thiopurines	90.9% (20/22)= clinical response; 63.63% (14/22)= clinical remission in 8 weeks
Hiraoka ⁽¹²⁾	2015	Japan	Moderate-to-severe colitis refractory to other treatments	CAI	24	Tacrolimus 0.1 mg/kg/day (adjusted by serum target level:10-15 ng/mL)	aminosalicilates; steroids; thiopurines	79% (19/24)= remission and/or response
Endo ⁽⁹⁾	2016	Japan	Steroid-dependent or refractory moderate-to-severe colitis	CAI up to 8 weeks	47	Tacrolimus 0.1 mg/kg/day (adjusted by serum target level:10-15 ng/mL)	aminosalicilates; steroids; thiopurines	68.08% (32/47)= clinical response; 55.31% (26/47)= clinical remission. 14.89% (7/47)= colectomy on follow up
Yamamoto ⁽³³⁾	2016	Japan	Steroid-dependent or refractory moderate-to-severe colitis	UC-DAI up to 12 weeks	50	Tacrolimus 0.1 mg/kg/day (adjusted by serum target level:10-15 ng/mL)	aminosalicilates; steroids; thiopurines	62% (31/50) = clinical response; 40% (20/50)= clinical remission
Nuki ⁽²³⁾	2016	Japan	Moderate-to-severe colitis	UC-DAI up to 10 weeks	21	Tacrolimus 0.1 mg/kg/day (adjusted by serum target level:10-15 ng/mL)	aminosalicilates; steroids; thiopurines	85.7% (18/21)= clinical response; 66.7% (14/21)= clinical remission in 10 weeks

UC: ulcerative colitis. DAI: disease activity index; CAI: colitis activity index.

Only two studies^(24,25) (Ogata 2006 and Ogata 2012) were randomized controlled trials. The features of these trials are shown in Table 2. Overall, 127 UC patients were included for meta-analysis. Table 3 shows the methodological analysis of these two trials. As witnessed in Figure 2, tacrolimus significantly increased the risk of clinical response versus placebo [RR of clinical response

failure 0.58 (0.45-0.73)], with a NNT of 3. Figure 3 highlights the RR of failure of clinical remission versus placebo, which was 0.91 (0.82-1), with a NNT of 10. Mucosal healing, as shown in Figure 4, was also significantly favoured by tacrolimus treatment [RR 0.59 (0.46-0.74)] with a NNT of 3. According to Egger test, a low risk of publication bias was found ($P>0.5$).

TABLE 2. Characteristics of randomized controlled trials included in meta-analysis

Author	Year	Country	UC severity and distribution	Remission definition (and time considered)	Number of patients	Interventions	Concomitant treatment
Ogata ⁽²⁵⁾	2006	Japan (17 centers)	Moderate-to-severe left colitis or pancolitis	DAI Score <2 with every subitem <1. Clinical response: a decrease of at least 4 points in DAI. Evaluation in 2 weeks and then open follow up up to week 12. Mucosal healing evaluated	65 patients randomized; 60 patients finished study: 19 in Tacrolimus group (high-dosage), 21 in Tacrolimus low-dosage group and 20 in placebo group	0.05 mg/kg b.i.d. (adjusted to serum target levels of 5-10 ng/mL or 10-15 ng/mL) versus placebo	Aminosalicilates and/or oral/IV steroids
Ogata ⁽²⁴⁾	2012	Japan	Moderate-to-severe, steroid-refractory left colitis or pancolitis	DAI Score <2 with every subitem <1. Clinical response: a decrease of at least 4 points in DAI. Evaluation in 2 weeks and then open follow up up to week 12. Mucosal healing evaluated	62 patients aleatorizados; 30 a rama placebo y 32 a rama tacrolimus	0.5-1 mg b.i.d. (adjusted to serum target levels of 10-15 ng/mL) versus placebo	Aminosalicilates and/or oral/IV steroids

UC: ulcerative colitis. DAI: disease activity index.

TABLE 3. Methodological analysis of randomized controlled trials included in meta-analysis

ID Study	Concealed random allocation	Blinding of patients and medical team	Similar interventions between groups	Complete follow up	Intention to treat analysis	Jadad score
Ogata 2006 ⁽²⁵⁾	Not clear	Yes	Yes	Yes	No	4
Ogata 2012 ⁽²⁴⁾	Yes	Yes	Yes	Yes	Yes	5

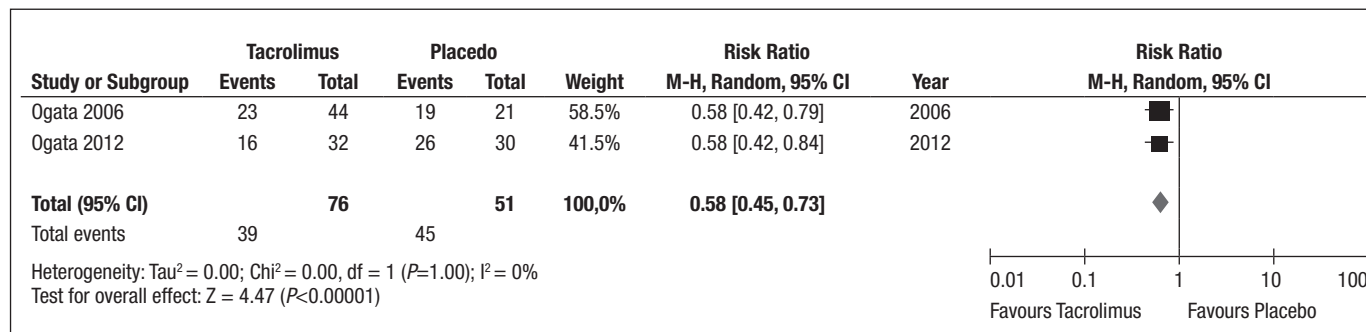


FIGURE 2. Forest Plot showing meta-analysis on clinical response of tacrolimus versus placebo.

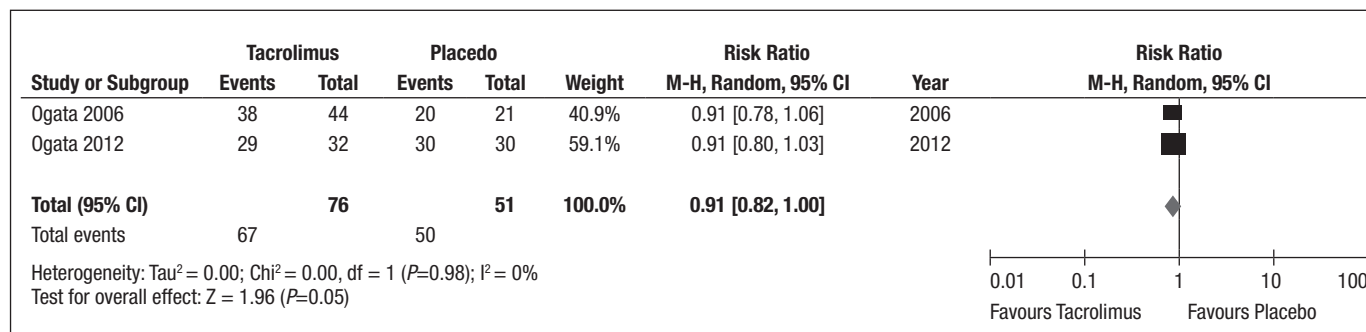


FIGURE 3. Forest Plot showing meta-analysis on clinical remission of tacrolimus versus placebo.

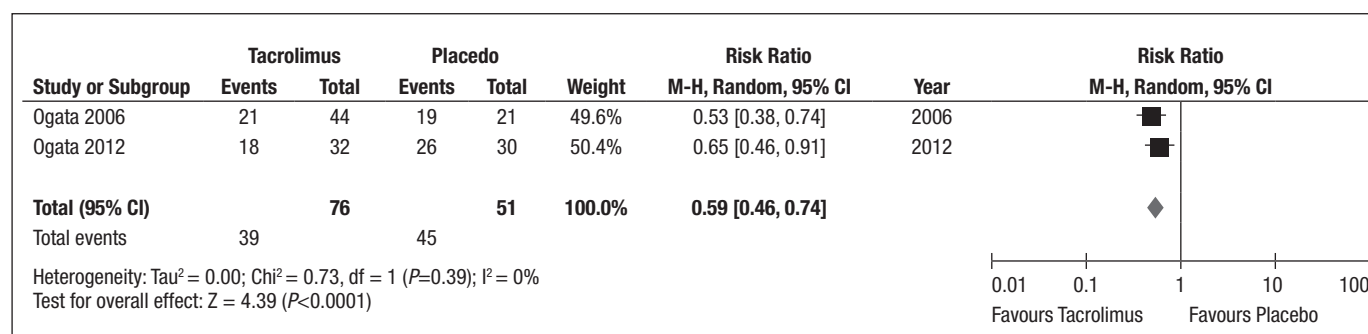


FIGURE 4. Forest Plot showing meta-analysis on mucosal healing of tacrolimus versus placebo.

The most commonly reported severe adverse events were gastroenteritis and sepsis. When considering only the randomized controlled trials, there was not a significant increase in the risk of serious adverse events versus placebo [RR 3.38 (0.17-68.91)].

DISCUSSION

According to the results observed in our systematic review, tacrolimus therapy could be a valid alternative in the context of moderate-to-severe UC that have not responded to other treatments or who are regarded as cortico-dependent or refractory.

As mentioned before, evidence on the efficacy of calcineurin inhibitors derives mainly from the experience of cyclosporine as a rescue therapy in the setting of severe UC. In a pioneer study, Lichtiger et al.⁽¹⁸⁾ showed that endovenous cyclosporine was useful to avoid colectomy in patients with severe UC flares after systemic steroid therapy failure. D'Haens et al.⁽⁸⁾ concluded that cyclosporine is a valid alternative to intravenous steroids in severe flares. Additionally, controlled studies have shown that cyclosporine may be equivalent to Infliximab in this type of clinical scenario⁽¹⁸⁾. Nevertheless, it should be reminded that cyclosporine has a non-neglectable adverse event profile and there is much less evidence apart from its parenteral use.

Tacrolimus is a well-known calcineurin inhibitor that is widely used as immunosupresant therapy in the context of transplant or even for the treatment of autoimmune conditions⁽³¹⁾. Tacrolimus has the advantage that it can be administered orally and that its serum concentration can be easily measured and adjusted to reach the adequate level in each case. The initial experience in UC patients was originated in referral centers from Japan, and then it was adopted by some centers in Europe. According to what is witnessed in uncontrolled studies, tacrolimus shows a high proportion of clinical response in the short-term, with a low NNT; however, when clinical remission is considered, such proportion is lower and more variable.

It is worth mentioning, according to what is observed from uncontrolled studies, the relatively high proportion of patients who would eventually require colectomy in spite of receiving tacrolimus^(4,5,10,13,28,32) (Fellermann 2002, Hogenauer 2003, Baumgart 2006, Benson 2007, Yamamoto 2008, Schmidt 2013). As a consequence, it

would seem like tacrolimus could delay the need for colectomy in a selected group of patients – those moderate-to-severe UC patients with prior failure to other therapeutic alternatives. It should also be mentioned that no study has considered tacrolimus therapy in patients with less severe disease.

There is a scarcity of high-quality trials to know the real impact of tacrolimus in the management of UC. As a matter of fact, as shown by this review, there has only been published two controlled trials^(24,25) (Ogata 2006 and Ogata 2012), with a relatively low number of patients and a rather short follow up time. One strength of these two trials is that mucosal healing was included as an outcome, which is known to be a relevant prognostic factor and a therapeutic target, particularly when it comes to UC⁽²⁶⁾. It is also worth mentioning that all studies assessed the efficacy of oral tacrolimus for the continued treatment of UC patients.

Evidence on the efficacy of calcineurin inhibitors in the setting of CD is more scarce: there are only a few controlled trials, mainly on patients with perianal disease, and few cohort studies⁽¹⁹⁾. Nevertheless, the relatively few alternatives in severe CD may turn tacrolimus into a valid therapeutic option, regardless of the few scientific evidence available.

Some limitations should be mentioned. First of all, there were few studies included for meta-analysis, so the conclusions should be cautiously interpreted. We decided not to perform meta-analysis with observational uncontrolled studies, because this represents a high risk for relevant biases, which could in turn produce a distortion in the conclusions derived from higher-quality studies. Last but not least, it is worth mentioning that most observational studies were retrospective, with the logical limitations that this implicate.

In conclusion, tacrolimus seems to show in both uncontrolled studies as well as in placebo controlled trials, a significant efficacy to induce clinical response and remission in moderate-to-severe UC. However, more evidence is undoubtedly needed to fully estimate the magnitude of its benefit.

Authors' contributions

Juan Lasa: bibliographic review, data analysis, statistical analysis, manuscript review. Pablo Olivera: bibliographic review, data analysis, manuscript elaboration.

Lasa J, Olivera P. Eficácia do tacrolimus para indução de remissão em pacientes com colite ulcerosa moderada a grave: uma revisão sistemática e meta-análise. *Arq Gastroenterol*. 2017;54(2):167-72.

RESUMO – Contexto – Há evidências que mostram que os inibidores de calcineurina podem ser úteis para o tratamento da colite ulcerativa severa. No entanto, há poucos dados sobre a eficácia do tacrolimus para indução de remissão neste cenário. **Objetivo** – Desenvolver uma revisão sistemática sobre evidências existentes sobre a eficácia clínica do tacrolimus para a indução de remissão em pacientes com colite ulcerosa de moderada a grave. **Métodos** – Realizada pesquisa bibliográfica de 1966 a agosto de 2016 usando MEDLINE, Embase, LILACS e Biblioteca Cochrane. Foram utilizados os seguintes termos MeSH: “doenças inflamatórias intestinais” ou “colite ulcerativa” e “inibidores da calcineurina” ou “tacrolimo” ou “FK506”. Foram considerados para revisão estudos que avaliaram a eficácia clínica do tacrolimus para a indução de remissão em pacientes adultos com colite ulcerosa. Uma meta-análise foi realizada com esses estudos incluídos que também fossem controlados por placebo e randomizados. Avaliou-se a resposta clínica, bem como remissão clínica e a cicatrização da mucosa. **Resultados** – No total, 755 referências foram identificadas, das quais 22 estudos foram finalmente incluídos. Apenas dois deles eram experimentações randomizadas e, placebo-controlada. Um total de 172 pacientes foram avaliados. Verificou-se um risco significativamente menor de falha na resposta clínica para tacrolimus versus placebo [RR 0.58 (0.45-0.73)]; Além disso, um menor risco de falha na indução da remissão também foi encontrado versus placebo [RR 0,91 (0,82-1)]. **Conclusão** – Tacrolimus parece ser uma alternativa terapêutica válida para a indução de remissão em pacientes com colite ulcerosa moderada a grave.

DESCRIPTORES – Doenças inflamatórias intestinais. Tacrolimo. Inibidores de calcineurina.

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