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Citation
Feuerstein, Joseph D., Mona Akbari, Elliot B. Tapper, and Adam S. Cheifetz. 2016. “Systematic review and meta-analysis of third-line salvage therapy with infliximab or cyclosporine in severe ulcerative colitis.” Annals of Gastroenterology : Quarterly Publication of the Hellenic Society of Gastroenterology 29 (3): 341-347. doi:10.20524/aog.2016.0032. http://dx.doi.org/10.20524/aog.2016.0032.

Published Version
doi:10.20524/aog.2016.0032

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Systematic review and meta-analysis of third-line salvage therapy with infliximab or cyclosporine in severe ulcerative colitis

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Background In patients with ulcerative colitis who fail corticosteroids and are treated with rescue therapy (e.g. infliximab or cyclosporine) but fail to respond, salvage therapy with infliximab or cyclosporine can be considered. We sought to assess the efficacy and safety of this third-line salvage therapy.

Methods We performed a meta-analysis of trials published in PubMed up to January 2015 relating to the use of third-line salvage therapy following failure of intravenous corticosteroids and infliximab or cyclosporine. Pooled outcome rates for each salvage strategy and pooled odds ratio comparing the two strategies were calculated using the random effects model. Heterogeneity was assessed by the Q and I² statistics.

Results The search strategy yielded 40 articles of which 4 were eligible for inclusion. Four articles assessed patients who were treated with infliximab after failure of cyclosporine and 2 articles assessed the use of cyclosporine after failure of infliximab. There were 138 patients using infliximab as a third-line salvage therapy and 30 patients using cyclosporine. When comparing these two strategies, there was no significant difference in clinical response (RR 1.03, 95% CI 0.7-1.46 P=0.87), clinical remission (RR 0.69, 95% CI 0.30-1.57 P=0.37), or colectomy at 12 months (RR 1.14, 95% CI 0.79-1.67 P=0.48). Similarly, there was no significant difference in total (RR 1.91, 95% CI 0.38-9.64 p=0.43) or serious adverse events (RR 1.18, 95% CI 0.34-4.07 P=0.80).

Conclusion While third-line salvage therapy may be efficacious in achieving short-term clinical response/remission, there remains a significant risk of colectomy and adverse events.

Keywords Ulcerative colitis, infliximab, cyclosporine, salvage therapy

Ann Gastroenterol 2016; 29 (3): 341-347

Introduction Ulcerative colitis (UC) is a chronic idiopathic inflammatory bowel disease that can be associated with severe flares requiring hospitalizations in up to 25% of patients [1]. While the majority of patients admitted with severe UC will respond to intravenous steroids, one-third will require rescue therapy with infliximab, cyclosporine, or colectomy [2].

Cyclosporine has been shown to be effective in 64-82% of patients with UC failing intravenous corticosteroids [3,4]. Infliximab was later shown to be effective in this situation with similar efficacy [5]. Recently, a randomized controlled trial of infliximab versus cyclosporine for rescue therapy found response rates of approximately 85% at 7 days, and sustained response of 40-50% with either drug three months later [6]. Nevertheless, a substantial number of patients fail rescue medical therapy. Many would argue that in this situation colectomy is the appropriate choice, but some patients wish to avoid surgery. There are a number of studies that have assessed the efficacy and safety of salvage therapy with infliximab or cyclosporine following the failure of the other medication. However, these studies are small and none are randomized trials to assess the true efficacy of this therapy [7-11]. The most recent UC guidelines from the European Crohn's and Colitis Organisation (ECCO) state that using salvage therapy with a third drug is associated with significant risks but this can be considered in highly selected cases and only in special referral centers [12].
Given the limited data regarding the efficacy and safety of third-line salvage therapy following initial treatment with either infliximab or cyclosporine for intravenous steroid-refractory UC, we sought to perform a systematic review and meta-analysis of the studies evaluating this situation with the primary outcomes of clinical remission and serious adverse events.

Materials and methods

We performed an online search using PubMed (National Center for Biotechnology Information) to identify papers published between 1960 and 2015 using infliximab or cyclosporine as third-line salvage therapy in patients with UC who failed intravenous corticosteroids and rescue therapy with infliximab or cyclosporine. Our search on PubMed was performed on January 1, 2015 with the following Mesh and text terms:

("Colitis, Ulcerative"[Mesh] OR "ulcerative colitis"[tiab] OR "ulcerative proctitis"[tiab] OR "proctosigmoiditis"[tiab] OR "left-sided colitis"[tiab] OR "pan-ulcerative colitis"[tiab] OR "colitis"[tiab]) AND ("Salvage Therapy"[Mesh] OR "salvage therapy"[tiab] OR "rescue therapy"[tiab]) AND ("infl iximab"[Supplementary Concept] OR "infl iximab"[tiab] OR "infl iximab exposed"[tiab] OR "infl iximab failure"[tiab] OR "infl iximab failures"[tiab] OR "infl iximab exposure"[tiab]) AND ("Cyclosporine"[Mesh] OR "cyclosporin"[tiab] OR "cyclosporine exposure"[tiab] OR "ciclosporin"[tiab] OR "cyclosporin exposed"[tiab] OR "ciclosporin exposure"[tiab])

This search resulted in 30 manuscripts. Each manuscript was reviewed to determine if the therapy involved was consistent with our study regarding third-line salvage therapy.

Inclusion criteria

Any article published and indexed on PubMed that assessed the use of infliximab or cyclosporine as third-line salvage therapy following the initial failure of intravenous corticosteroids and rescue therapy with infliximab or cyclosporine. In order to be included, the use of the third-line agent had to be within 60 days of cessation of the prior drug.

Exclusion criteria

Articles not indexed on PubMed were excluded. Abstracts only presented at a medical conference but not published as a manuscript were not included. Additionally, case reports of only a single patient and review articles were also excluded.

Outcomes

Our primary outcomes were clinical remission and serious adverse events associated with each drug and in aggregate. Secondary outcomes included clinical response and 12 month colectomy rates.

Data extraction

Articles were reviewed independently by two authors (JDF, MA) for publication date, type of salvage therapy (infliximab, cyclosporine) number of patients, response, remission, failure/ colectomy, and any complications. Clinical remission was defined as normalization of bowel movement to <4/day without bleeding and off corticosteroids. Serious adverse events were infection or death.

Quality assessment

Given the few studies that were available on this topic, all studies were included.

Statistical analysis

Pooled estimates of primary and secondary outcome response rates for third-line salvage therapy were calculated using the random effects model. Similarly, the random effects model was used to calculate pooled odds ratio and 95% confidence intervals (CI) for studies that compared outcomes between the two third-line salvage therapies. Heterogeneity was assessed by the Q and I² statistics. All analysis was performed using STATA (Version 12.0; STATA Corporation, College Station, TX, US).

Results

Our PubMed search yielded 40 articles of which 5 specifically evaluated third-line salvage therapy in severe refractory hospitalized UC (Fig. 1) [7-11]. One manuscript was a case report of a single patient and therefore excluded from further analysis [8]. The remaining four articles included patients treated with infliximab following failure of cyclosporine [7,9-11]. However, only two of the articles, Maser et al and Leblanc et al, also included patients who were switched to cyclosporine after failing infliximab [9,10]. There were 138 patients who received infliximab and 30 patients treated with cyclosporine as a third-line salvage therapy. In each of the studies, patients were retrospectively evaluated from 2000-2008. Maser et al was a single-center US study whereas the other studies were multi-center studies performed in Europe. All the studies were designed retrospectively. See Table 1 for full demographics of the study populations.

Infliximab following cyclosporine as third-line salvage therapy

In the studies assessing salvage therapy with infliximab following cyclosporine usage, the mean age of the patients was 35 and 41% (57/138) were female. The average duration of disease was 3.8 years. However, the European studies had...
a mean disease duration of 2.2 years compared to 8.6 in the United States study. Sixty-six percent of patients (91/138) had extensive colitis and 49% (67/138) were previously or concomitantly on a thiopurine or methotrexate. There was a mean of 11 days (range 2-19) between the last dose of cyclosporine and the initial dose of infliximab.

The pooled clinical response and remission event rate for infliximab as third-line salvage therapy was 68% (95%CI 57-79%) and 41% (95%CI 24-58%) respectively at 3 months. The 12-month colectomy event rate was 41% (95%CI 27-55%) (Fig. 2). Of the 138 patients in these studies, when assessed in aggregate, 3 patients died (2.2%) and 14 patients (10.1%) developed an infectious complication during the study period (Table 2). Other complications included leukopenia, infusion reaction, skin rash, renal abnormalities, and small bowel obstruction. The serious adverse event rate was 9% (95% CI 4-14%), while the overall adverse event rate was 21% (95%CI 14-28%) (Fig. 2).

Cyclosporine following infliximab as third-line salvage therapy

In the two studies assessing salvage therapy with cyclosporine following infliximab therapy the mean age of the patients was 42 and 43% (13/30) of patients were female. The average duration of disease was 6.7 years and the majority of patients (77%, 23/30) had extensive colitis. Seventy-three percent (22/30) of patients were previously or concomitantly on a thiopurine or methotrexate. There was a mean of 20 days (range 19-21) between the last dose of infliximab and starting cyclosporine.

The overall response and remission event rates was 60% (95% CI 43-78%) and 18% (95%CI 4-31%) respectively at three months. The 12-month colectomy event rate was 57% (95%CI 39-74%) (Fig. 3).

There were no deaths among patients observed in these studies, but 10% (3/30) of all the patients developed an infectious complication (Table 2). Other complications included renal and hepatic abnormalities, fatigue, leg cramps, weakness, cough, and pancreatitis. The serious adverse event rate was 12% (95%CI 0.01-23%), and total adverse event rate was 31% (95%CI 16-47%) (Fig. 3).

Comparison of third-line salvage therapies

Given that only two studies reported results on patients receiving salvage therapies with cyclosporine following infliximab and infliximab following cyclosporine the overall data was extremely limited. Meta-analysis comparing these two strategies did not demonstrate a significant difference in achieving clinical response (RR 1.03, 95%CI 0.7-1.46; P=0.87), remission (RR 0.69, 95%CI 0.30-1.57; P=0.37), or 12-month colectomy (RR 1.14, 95%CI 0.79-1.67; P=0.48) (Fig. 4). Similarly, there was no difference in serious adverse events (RR 1.18, 95%CI 0.34-4.07; P=0.80) or total adverse events (RR 1.91, 95%CI 0.38-9.64; P=0.43) (Fig. 4).
Third-line salvage therapy with either infliximab or cyclosporine is of great interest as approximately 60% of patients may fail initial rescue therapy following a lack of response to intravenous steroids [6]. In our meta-analysis of the literature, the choice of infliximab or cyclosporine as a third-line agent did not provide any significant difference in response, remission, colectomy, or adverse events. Overall, 41% of patients achieved an initial remission when using infliximab as a third-line therapy which compared to an 18% remission rate in those using cyclosporine as a third-line agent. However, by 12 months 41% of patients treated with infliximab and 57% of patients who received cyclosporine required colectomy. Additionally, both agents were associated with significant adverse events when used as a third-line agent (9% for infliximab and 12% for cyclosporine).

While many are intrigued by the idea of third-line salvage therapy, the overall benefits and safety of this option remain unclear. When considering the initial use of salvage therapy in patients failing intravenous steroids, Laharie et al randomized patients to either infliximab or cyclosporine and noted treatment failure in 54-60% of cases within 3 months [6]. Interestingly, in our study, additional salvage therapy with a third agent failed to achieve remission in 60-80% of cases. Furthermore, colectomy was still the outcome in 40-57% of the patients despite the use of a third-line therapy. Ultimately, the utility and risk benefit analysis of using a third-line salvage therapy is unclear at this time.

The decision regarding a third-line salvage therapy is usually urgent with colectomy being the only other option. Given the severely active disease, the ability to allow the prior drug to washout of the patient's system is usually not feasible. In our meta-analysis, the average interval between cyclosporine to Table 2 Complications of therapy

| Total % (n) | Death % (n) | Infection % (n) | *Other complications % (n) |
|------------|-------------|-----------------|---------------------------|
| Cyclosporine → Infliximab n=138 | 22% (30) | 2% (3) | 10% (14) | 11% (15) |
| Infliximab → Cyclosporine n=30 | 10 (33%) | 0 | 4 (13%) | 6 (20%) |

*Other complications include: Infusion reaction, skin rash, small bowel obstruction, Infliximab salvage: death gram negative sepsis, Cyclosporine salvage: pancreatitis, herpes esophagitis

**Figure 2** Pooled response, remission, colectomy and adverse events for third-line cyclosporine to infliximab salvage therapy

**Discussion**

Third-line salvage therapy with either infliximab or cyclosporine is of great interest as approximately 60% of patients may fail initial rescue therapy following a lack of response to intravenous steroids [6]. In our meta-analysis of the literature, the choice of infliximab or cyclosporine as a third-line agent did not provide any significant difference in response, remission, colectomy, or adverse events. Overall, 41% of patients achieved an initial remission when using infliximab as a third-line therapy which compared to an 18% remission rate in those using cyclosporine as a third-line agent. However, by 12 months 41% of patients treated with infliximab and 57% of patients who received cyclosporine required colectomy. Additionally, both agents were associated with significant adverse events when used as a third-line agent (9% for infliximab and 12% for cyclosporine).
infliximab was 11 days and the interval between infliximab to
cyclosporine was 20 days. The data regarding the efficacy and
safety of an immediate transition from one drug to the next
is extremely limited. Therefore, the generalizability of these
studies to patients who were just dosed with either cyclosporine
or infliximab with a plan to salvage with a third-line drug is
unclear. It is possible that the risk of serious adverse events may
be even higher in this setting given the immunosuppression
with corticosteroids, combined with the recently stopped
immunosuppressive agent, and with the new added third-line
salvage drug. Already, our study notes that the risk of serious
adverse events is high even with a small washout period of
11-20 days. As a result, it is yet another reason to be extremely
cautious when considering the use of third-line salvage therapy
as an option.

When using rescue therapy for steroid refractory UC,
Laharie et al reported complication rates of 16% in patients
treated with cyclosporine and 25% in those treated with
infliximab [6]. When these agents are then used as third-line
salvage therapy we found a similar risk of serious adverse events
of 9% with infliximab and 12% with cyclosporine. Though there
was no significant difference in complications 2% of patients
treated with infliximab following cyclosporine died compared
to no deaths reported in the group that received cyclosporine
following infliximab [13]. It is unclear if this is truly related to
cyclosporine third-line therapy being safer or just due to the
limited number of patients (n=30) given cyclosporine after
infliximab. What is especially concerning about the mortality
associated with third-line therapy, is that this mortality rate is
slightly higher than what is reported following colectomy in
the setting of acute severe UC [14]. To use a drug that carries
a higher rate of death compared to colectomy raises important
questions regarding the safety of this option.

As new drugs become available to treat UC, it remains
unclear if any will be effective as rescue therapy options.
Currently, vedolizumab, an anti α4/β7 integrin monoclonal
antibody, is the newest drug available to treat UC [15].
While its overall efficacy in treating UC is clear, the utility
of this drug in the setting of a severe flare is unlikely to
be effective. The drug works by antagonizing the integrin
receptor and thereby blocking lymphocyte migration to the
gastrointestinal mucosa [15,16]. It does not however treat the
active inflammatory process quickly which is needed in cases
of steroid refractory UC [16]. Ultimately, new drugs are needed
that work on the active inflammatory process to further the
armamentarium from the current two drug option when
failing rescue therapy.

As with any meta-analysis, our study has a number of
limitations most of which are due to the nature of the studies
reviewed. All the manuscripts included in our study were
retrospective. The total number of patients in the cyclosporine
salvage therapy following infliximab was smaller and included
in only two studies somewhat limiting our comparison
between the groups. Additionally, the study follow up time

Figure 3 Pooled response, remission, colectomy and adverse events for third-line infliximab to cyclosporine salvage therapy
period between studies was variable limiting the ability to provide response and remission rates at 12 months.

In conclusion, third-line salvage therapy with either cyclosporine or infliximab is efficacious in some patients but carries a significant risk of complications. Importantly, 41-57% of these patients will end up requiring a colectomy within 12 months. Future studies are needed to prospectively evaluate the benefits and risks of this strategy compared to colectomy.

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