Original article

Efficacy of Cytapheresis for Remission Induction and Dermatological Manifestations of Ulcerative Colitis

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Running head: Cytapheresis for induction therapy in UC

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Abstract

Background: In ulcerative colitis (UC) patients, cytapheresis depletes elevated and activated leucocytes, which are known to release inflammatory cytokines including tumour necrosis factor (TNF)-α. Further, there are UC patients who develop erythema nodosum (EN) or pyoderma gangrenosum (PG) as extra-intestinal manifestations.

Methods: Between 2008 and 2015, 181 consecutive patients with active UC received cytapheresis with either a granulocyte and monocyte apheresis (GMA) column or with a leucocyte removal filter (LCAP) as remission induction therapy. Each patient received weekly or intensive (2-3 sessions/week) cytapheresis up to 10 sessions. In 13 patients, UC was complicated by EN or PG. Lichtiger's clinical activity index (CAI) ≤4 meant remission, while ≥3 decrease in CAI meant response to therapy. Prednisolone sparing and the changes in the extra-intestinal manifestation were factored for assessing treatment efficacy.

Results: The overall remission and response rates were 52.5% and 71.8%, respectively, CAI fell from 9.4±3.3 to 4.9±3.5 ($P<0.001$). The efficacy rates in subgroups on concomitant corticosteroid, anti-TNF or tacrolimus and those without concomitant medications were not significantly different ($P>0.05$). However, in 84 patients on prednisolone, the average daily prednisolone dose was reduced from 18.15mg to 12.43mg ($P<0.001$) with 21.7% being corticosteroid free. All 13 patients with EN or PG showed favourable response to cytapheresis, notably 2 EN patients showing complete remission after just 2 cytapheresis sessions without concomitant medication,

Conclusions: In this retrospective efficacy evaluation, cytapheresis was effective as remission induction therapy with steroid sparing effect and desirable safety profile. Further, patients with EN or PG responded favourably to cytapheresis.

Keywords: Ulcerative colitis; Extra-intestinal manifestation; Granulocytes and monocytes; Cytapheresis; Remission induction therapy; Erythema nodosum; Pyoderma gangrenosum; Prednisolone, Tacrolimus, Anti-TNF-α

INTRODUCTION

Ulcerative colitis (UC) is one the two major phenotypes of the chronic inflammatory bowel disease (IBD) affecting the lower gastrointestinal tract with a relapsing and remitting course. The other major phenotype of IBD is Crohn's disease (CD), which is not covered in this article. UC is typically manifested as contiguous inflammation involving the intestinal mucosa and submucosal layers, primarily in the large intestine (rectum and the colon). Further, in up to 30% of UC patients, extra-intestinal manifestations affect various organs including joints, skin, liver, eyes, and mouth, which either precede the onset of symptoms or appear and evolve in parallel with the intestinal manifestations of UC.[1] Erythema nodosum (EN) and pyoderma gangrenosum (PG) are the two major cutaneous ills of extra-intestinal manifestations of UC.[2]

However, in recent years, ground breaking progress has been made in the treatment of patients with UC. The anti-tumour necrosis factor (TNF)-α antibodies like infliximab (IFX) have indicated that mucosal healing is a key therapeutic goal, and may predict the sustainability of remission and resection-free survival in patients with UC. These findings led to the approval of IFX in 2010 as an alternative medication for refractory UC in Japan. However, as remission induction therapy for steroid-refractory UC, currently several treatment options are available in Japan, which include cytapheresis, and tacrolimus in addition to anti-TNF-α biologics. However, as yet, there is no guideline for the sequence and timing of these therapeutic interventions. Additionally, there are many patients who do not respond to anti-TNF-α biologics or initially respond and then experience loss of response. Recently, apheresis, which means 'to take away' the extra-load of activated leucocytes from the patients' circulation by

using an extracorporeal system has been applied as a feasible, safe and effective therapy for most patients with IBD. Currently, two methods are commercially available and used in clinical practice setting for therapeutic leucocytapheresis in patients with IBD or rheumatoid arthritis. These are the Adacolumn for selective granulocytes and monocytes apheresis (GMA) developed by JIMRO (Takasaki, Japan) and leucocytapheresis (LCAP) with the Cellsorba filter column (Asahi, Tokyo, Japan). This study was to assess the efficacy of cytapheresis for remission induction, hospitalisation avoidance, prednisolone sparing and dermatological manifestations of UC.

METHODS

Patients

Between 2008 and 2015, a total of 181 patients received cytapheresis as remission induction therapy for active UC at the Department of Gastroenterology, Juntendo University Hospital in Tokyo. The therapeutic outcomes in these 181 patients were reviewed in a retrospective setting. Patients' major demographic variables at entry are presented in Table 1. In 13 patients, UC was complicated by skin lesions like EN or PG. Each patient received weekly or intensive (2-3 sessions/week) cytapheresis up to 10 sessions as one treatment course, with either a granulocyte-monocyte apheresis (GMA) column or with a leucocyte removal filter (LCAP) as previously described by Sakata, et al.[3] Among the 181 patients, 103 were on concomitant medications during the cytapheresis course, including prednisolone, anti-TNF biologic or tacrolimus.

Measurement of disease activity, and efficacy

Patient's UC disease activity was evaluated according to the using the clinical

activity index (CAI) described by Lichtiger, et al.[4] CAI ≤4 meant clinical remission, while ≥3 decrease in the CAI score relative to baseline meant clinical response. Corticosteroid dose was to be tapered in responders. Clinical end-points were evaluated after the cytapheresis course and included remission induction rate, hospitalisation avoidance, corticosteroid dose decrease or discontinuation, changes in EN and PG. Hospitalisation avoidance was defined as patients with severe UC (CAI ≥11) who received cytapheresis therapy in an outpatient setting. Corticosteroid sparing was defined as patients with a CAI of ≥5 within one month after the cytapheresis course, but could avoid corticosteroid. Corticosteroid dose tapering was evaluated as the dose change between before and after the cytapheresis course. With regard to skin lesions including EN and PG, an improvement of lesions and symptoms was defined as partial response, while total disappearance of the lesions after treatment was defined as complete response.

Statistical analysis

When appropriate, numerical data are presented as the mean ± SD values. The Mann-Whitney U-test was applied for statistical analyses of the data, comparing CAI and corticosteroid dosage between before and after cytapheresis treatment course. The clinical efficacy and safety data were assessed by using the Chi-square test for categorical variables. Differences for a P-value <0.05 were considered statistically significant.

RESULTS

The overall efficacy of cytapheresis as remission induction therapy

Among the 181 patients, 78 were male and 103 were female, mean age 38.3± 12.6 years, range 17-65 years. In all 181 cases who received cytapheresis as remission

induction therapy, the clinical remission and response rates were 52.5% (95 patients) and 71.8% (130 patients, including those who achieved remission), respectively. As seen in **Figure 1**, the overall CAI score decreased from 9.4±3.4 to 4.9±3.5 (n=181, P<0.001). The clinical response rates **(Figure 2)** in subgroups on concomitant and without concomitant medications were 77.7% (80 of 103 patients) and 64.1% (50 of 78 patients), respectively, not significantly different (P=0.28, by Fisher's exact test. Likewise, the clinical remission rates with concomitant and without concomitant medications were 57.3% (59 of 103 patients) and 46.2% (36 of 78 patients), respectively (P=0.13, by Fisher's exact test. Therefore, our retrospective evaluation did not show significantly better efficacy rate in the patients who received cytapheresis while being on concomitant medications vs patients who received cytapheresis as monotherapy.

Regarding hospitalization due to severe UC, the avoidance rate was 93.5% or 29 of 31 patients with severe UC (CAI ≥11). All these 29 patients received cytapheresis in an outpatient setting. Additionally, 15 of 16 patients in the severe UC subgroup responded well to cytapheresis as monotherapy **(Figure 3)**. Similarly, corticosteroid avoidance was achieved in 85 of 98 patients (86.7%) who were with moderate to severe UC, and steroid naïve, but by receiving CAP therapy, they could avoid receiving corticosteroids. Further, in the patients who were taking corticosteroid, the total corticosteroid dose (mean ±SD) decreased from 18.15±14.13 at entry to 12.43±11.40 (P<0.001) at post cytapheresis course **(Figure 4).** Corticosteroid discontinuation within one month after the cytapheresis course was achieved by 18 of 83 patients (21.7%) seen in **Figure 4**.

Efficacy of cytapheresis on skin lesions.

Thirteen patients had skin lesions associated with UC, EN (n=6) and PG (n=7). All 13 patients with extra-intestinal complications showed a marked improvement at post cytapheresis course. Notably, 2 patients with EN showed rapid remission after the first 2 cytapheresis sessions without being on any concomitant medication, but 7 of the 13 patient (1 EN and 6 PG) were on concomitant steroid or IFX **(Figure 5)**. In Figure 6, photographs from skin lesions in a typical responder patient are presented.

Safety of cytapheresis

Non-serious, transient adverse events during cytapheresis were observed in 7 patients (3.86%), including lightheadedness, facial flushing, mild headache, fever and tiredness. All these events remitted within a few hours following the end of the cytapheresis session without requiring medications.

In Figure 7, a tentative treatment algorithm pertained to patients with UC in whom UC is complicated by PG or EN as extra-intestinal manifestation of UC or otherwise as an additional morbidity. Patients receive a 5-aminosalicylate (5-ASA) preparations as a first-line medication. Non-responders may receive cytapheresis (CAP) as monotherapy. Corticosteroids or an anti-TNF biologic may be added to CAP if complete remission was not achieved with CAP monotherapy. The dose of pharmacologics may be tapered gradually or discontinued when patients achieve remission or improve.

DICUSSION

In Japan, cytapheresis is a recommended and officially approved therapy for

patients with active UC, which is refractory to pharmacological. In this study, the efficacy of cytapheresis was retrospectively evaluated in a large number of consecutive patients treated at our university hospital over several years. We found an efficacy rate of about 70%, which is close to the level, which is in line with efficacy outcomes reported in this clinical setting.[5,6] Further, considering cytapheresis in IBD patients, which is a cell removal treatment intervention, selectivity is essential because although patients have activated and often elevated myeloid lineage leucocytes (granulocytes and monocytes), lymphocytes are compromised,[7] and should be spared. In fact, an elevated granulocyte÷lymphocyte ratio was found to predict clinical relapse in UC setting (7). Likewise, patients with severely active UC may lose blood via bleeding ulcers and therefore patients' red cells should not become part of the cell removal mechanism of cytapheresis. To our knowledge, GMA spares lymphocytes sand virtually no red cell is lost,[8,9] but LCAP, which uses a cell trapping filter removes lymphocytes and some red cells as well.[3]

Regarding drug therapy in patients with active UC, while mild cases of UC may respond to 5-aminosalicylate preparations as induction therapy as well as for maintenance of remission, management of patients with severe UC is a major therapeutic challenge, especially in cases with steroid dependent, or steroid refractory UC and patients who are intolerant to corticosteroids. Some of such patients may respond to cytapheresis and be spared from drug therapy. Matsumoto, et al. analyzed 105 patients with moderate to severe UC (10). Fifty-six rapid responders (53%) achieved remission within 3 weeks of the start of cytapheresis and the responder rate was 74% with 64% achieving clinical remission. However, with GMA, efficacy rates vary from an 85%[11-13] to a

statistically insignificant level.[14] Patients' entry demographic features are known to identify responders and non-responders to cytapheresis.[11] In this retrospective endeavor, clinical remission and response rates were 53.6% and 71.3%, respectively. However, in spite of very favourable safety profile associated with cytapheresis, corticosteroids remain the mainstay of therapy for active UC. The major limitation of corticosteroids is that at high doses over a long period of time are associated with predictable and potentially serious side effects.[15,16]

It was intriguing for us to see that our retrospective evaluation of treatment outcomes did not show an impact for concomitant medications on efficacy rate. We found that clinical response and remission rates in subgroups on concomitant medications, which included corticosteroid, anti-TNF biologic or tacrolimus and the subgroups not on these medications were not significantly different. What might this mean? The most likely assumption was that prior to the entry to cytapheresis therapy, patients had been on these medications for some time, and had not responded, were with active UC. Accordingly, the efficacy we factored into our analysis was attributable to cytapheresis per se. In line with our findings, Ashida, et al.[17] carried out a multicentre study to investigate the efficacy of leucocytapheresis without concomitant steroid. Of the 20 patients in that study, 15 (75%) responded with 7 (35%) achieving complete remission.

Perhaps, corticosteroid sparing action of cytapheresis is very favourable by both patients and the physicians who often bear concerns about long term side effects of medications in patients with IBD.[18] In most patients with mild to moderate UC, cytapheresis as monotherapy should induce clinical remission. In line with this thinking, our retrospective review showed that corticosteroid sparing was

achieved in 85 of 98 patients who were with moderate to severe UC, but had achieved remission without receiving corticosteroids. Further, in the patients who were taking corticosteroid prior to and during the course of cytapheresis, the total corticosteroid dose was tapered by about one-third as assessed at the post cytapheresis course including 18 patients who had become corticosteroid free.

Extra-intestinal manifestations are relatively common in UC and affect joints, skin, eyes, bile ducts, and various other organs.[19] EN is the most common cutaneous form and affects 3 to 10% of all patients with UC and 4 to 15% of patients with CD.[20-22]. When EN develops in UC patients, it is typically associated with exacerbation of the colitis even if the severity of EN does not necessarily parallel the severity of the underlying bowel disease.[23] However, in situations where lesions occur during the quiescent phase of IBD, systemic steroids have been applied.[24] In resistant or highly relapsing cases, TNF-α antagonists have been used.[25] Regarding the efficacy of cytapheresis, 2 of 6 EN patients showed rapid remission after the first 2 cytapheresis sessions without any concomitant medication. The non-responder patient had responded to biologics because the intestinal manifestations were severe. PG represents the second most common cutaneous manifestation of IBD, and can be more debilitating than the bowel disease itself.[26-29] Recently, anti-TNF-α biologics have been used in steroid-refractory PG.[30,31] We applied cytapheresis to UC with PG which was refractory to medications that patients had been on for their UC. Cytapheresis showed a marked efficacy in 12 of 13 patients with EN or PG without any safety concern.

Regarding the positioning of cytapheresis in the treatment of patients with UC (as

well as CD), up to now, when a patient experiences a relapse, initially 5-aminisalicylate (5-ASA) preparations at an already known optimum dose is given. If a salicylate did not induce remission, oral corticosteroid is an option. In cases with severe UC, intravenous corticosteroid is more likely to induce rapid remission than an oral dose. Anti-TNF biologics and tacrolimus are other options, but have safety concerns. However, our opinion is that cytapheresis should be the first choice in first episode cases as well as in drug naïve cases. Patients who receive cytapheresis at an early stage of their IBD are known to respond well to a second course of cytapheresis upon a relapse.[32-34] One advantage of cytapheresis is that extra-intestinal lesions may also respond along with a fall in CAI. There are also patients who are intolerant to certain pharmacologicals or wish not to receive corticosteroids. These include ladies who have family planning in mind, paediatrics/adolescents, and elderly patients. In such cases cytapheresis might be the treatment of choice. Lets' not forget that some patients do not respond to cytapheresis as well. We believe that baseline demographic features should identify the most likely responders to cytapheresis. A tentative treatment algorithm is presented in Figure 6.

At this point, we like to acknowledge specific limitations of this study. Firstly, it was a retrospective undertaking at a single academic centre. This means, it was not possible to fully evaluate the contribution of concomitant medications on the efficacy of cytapheresis. Secondly, we had access only to the patients who had undergone cytapheresis therapy for active UC at our institution. We believe that data from a randomized, double blind multicenter study more accurately shows the efficacy of cytapheresis. Similarly, the efficacy of cytapheresis on extra-intestinal manifestation should be in a multicenter double blind randomized

trial. Therefore, further investigation is necessary to evaluate the true efficacy of cytapheresis for patients with UC showing extra-intestinal manifestations.

In conclusion, in this retrospective efficacy evaluation undertaking, we found that cytapheresis was associated with good efficacy as remission induction therapy together with significant corticosteroids sparing effect. Additionally, patients with extra-intestinal manifestations like EN and PG responded well to cytapheresis. Here we like to acknowledge that cytapheresis is very much favoured by patients as well as by the physicians for its good safety profile as well as for being a non-pharmacologic treatment intervention. Accordingly, in this relatively large population of 181 patients, no serious adverse event related to cytapheresis was observed. As cytapheresis is a non-drug treatment strategy, refractoriness, intolerance and loss of response often experienced during drug therapy are not likely. We like to suggest that future studies should look for entry demographic features, which potentially identify a patient as a likely responder to cytapheresis or otherwise as a non-responder. In clinical settings such information should help to make a more efficient use of cytapheresis, and avoid wasting resources.

Authors' contribution

All authors were involved in the conduct of this study, had full access to the study data, and contributed to the preparation of the manuscript as follows. O. Nomura, T. Osada, and T. Shibuya: Study concept, design, and drafting of the manuscript; D. Ishikawa, K. Haga, and T. Kodani: Endoscopy, and patients evaluations; O Nomura, N. Sakamoto, T. Ogihara, S. Watanabe: Data acquisition and statistical analyses of the data; O. Nomura, T. Osada, T. Shibuya, D. Ishikawa, K. Haga, T.

Kodani, N. Sakamoto, T. Ogihara, S. Watanabe: Interpretation, critical revision of the manuscript for important intellectual content and approval of the final manuscript version for submission.

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Competing interest: None

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Figure legends

Figure 1. This figure shows the overall change in the clinical activity index (CAI) in all 181 ulcerative colitis (UC) patients who received cytapheresis (CAP) as remission induction therapy. The overall CAI score decreased from 9.4±3.4 at baseline to 4.9±3.5 post CAP treatment course ($P<0.001$).

Figure 2. The clinical response based on ≥3 point decrease in the clinical activity index (CAI) relative to baseline, and remission rates for cytapheresis (CAP) therapy in 181 ulcerative colitis (UC) patients were 71.3% (including patients with remission) and 53.6% respectively. In the CAP alone subgroup, the response rate was 65.6%. Other medications included prednisolone, an anti-TNF biologic, or tacrolimus.

Figure 3. Efficacy outcomes for cytapheresis (CAP) therapy in 31 patients with severe ulcerative colitis (UC) most of whom were treated in an outpatient setting. The clinical response and remission rates were 77.5% and 45.2%, respectively.

Other medications included prednisolone, an anti-TNF biologic, or tacrolimus.

Figure 4. This figure shows the corticosteroid sparing effect of cytapheresis (CAP) in ulcerative colitis (UC) patients. Among the 83 patients who were on prednisolone at entry, 18 became steroid free (discontinued prednisolone) one month after the end of CAP course. In addition, 85 of 98 steroid naive patients could avoid prednisolone during the time course of our treatments and observations; the corticosteroid avoidance rate was 86.7%.

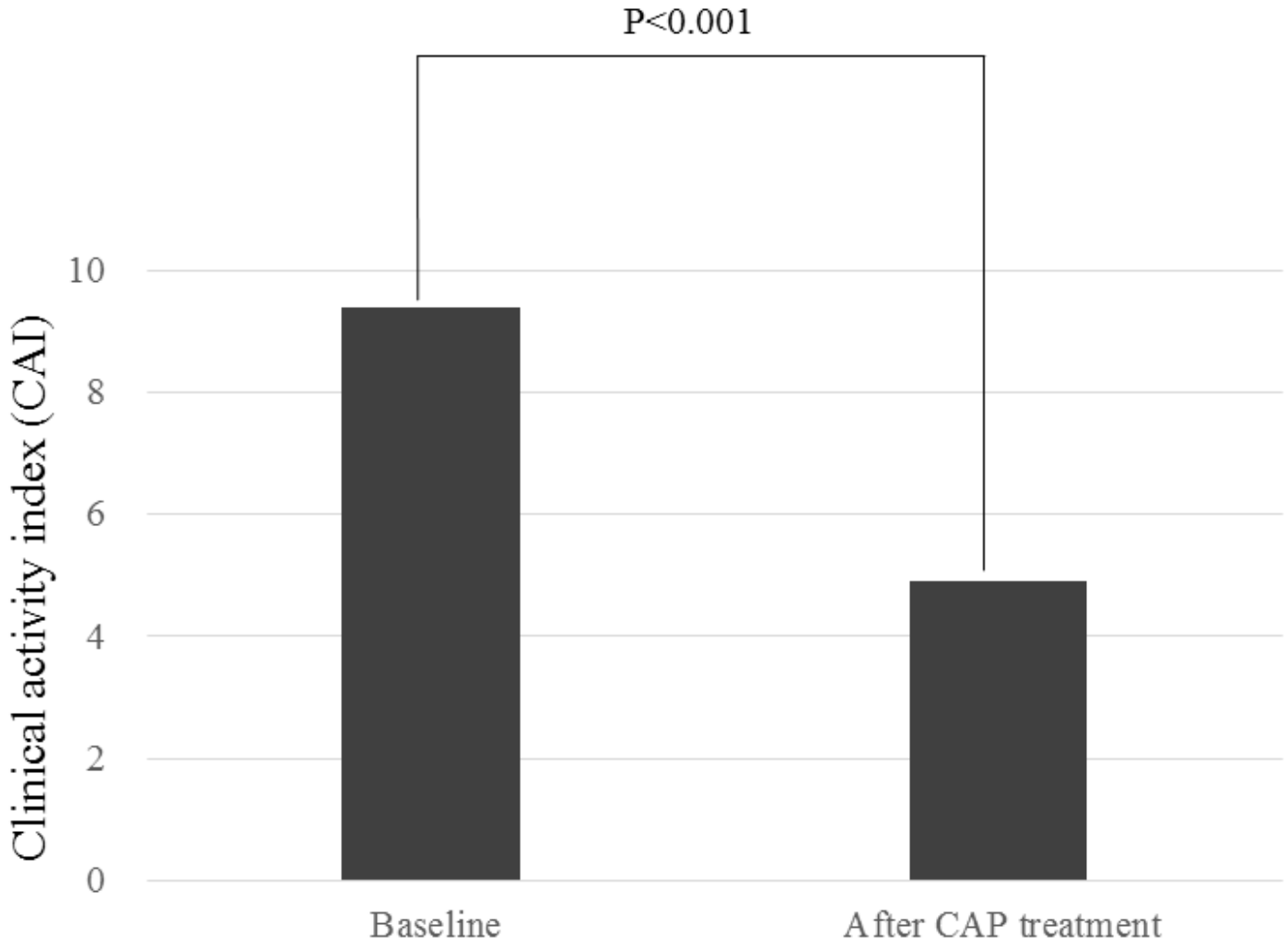
Figure 5. This figure shows the therapeutic outcome of cytapheresis (CAP) in a subgroup of 13 patients in whom ulcerative colitis (UC) was complicated by extra-intestinal manifestations as dermatoid lesions including erythema nodosum (EN), and pyoderma gangrenosum (PG). Patients received concomitant medications with infliximab (IFX), prednisolone (PSL) or CAP monotherapy. Complete responder meant disappearance of EN and PG, while partial responder meant improvement or reduction of the skin area affected by EN or PG.

Figure 6. This figure shows typical dermatological efficacy of cytapheresis (CAP) in patients in whom ulcerative colitis (UC) was complicated by erythema nodosum (EN) or pyoderma gangrenosum (PG). This case was among a few who achieved complete remission.

Figure 7. This figure shows a tentative treatment algorithm pertained to patients with ulcerative colitis (UC) in whom UC is complicated by pyoderma gangrenosum (PG) or by erythema nodosum (EN) as extra-intestinal manifestation of UC or otherwise as an additional morbidity. Patients receive a

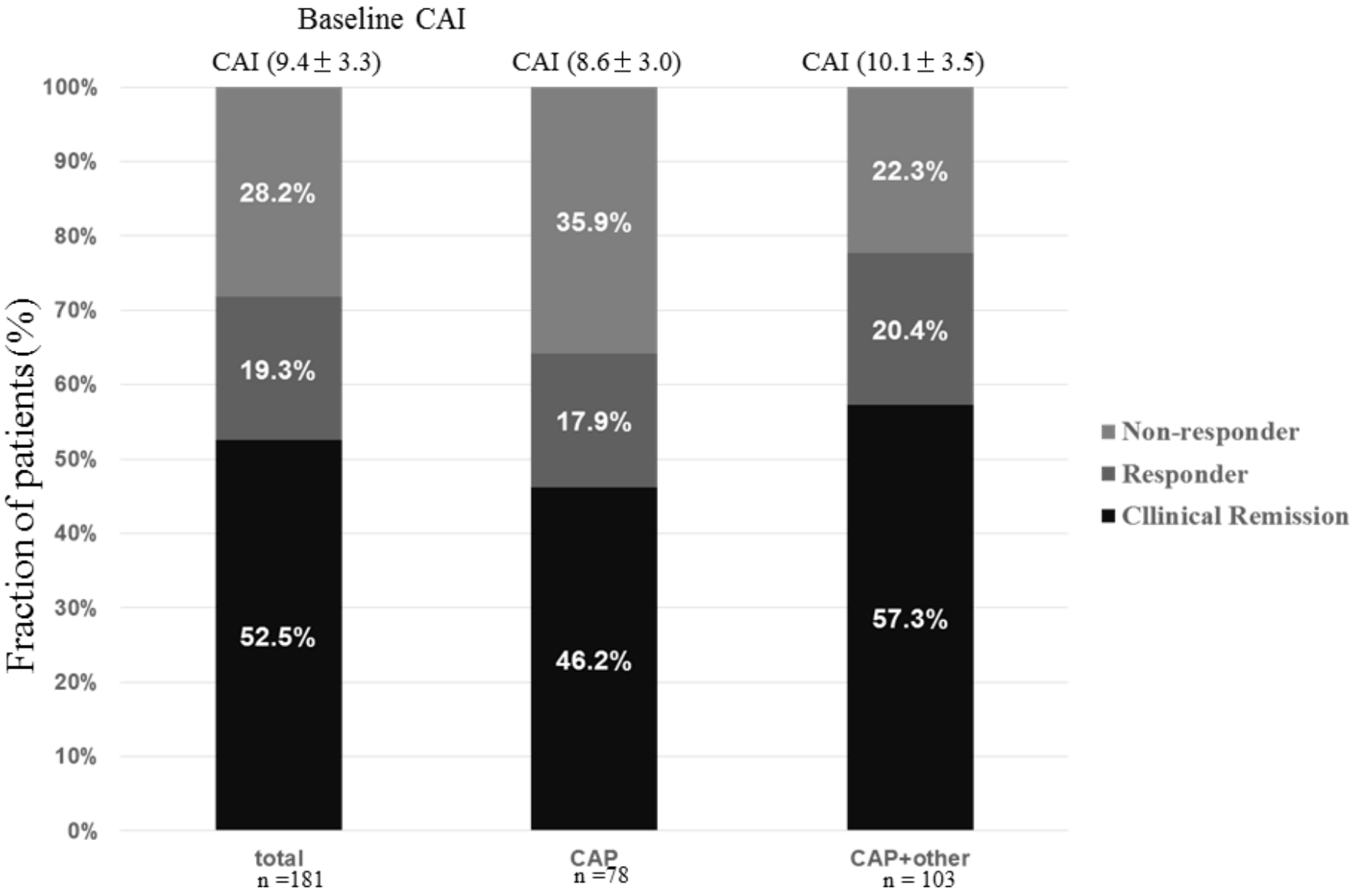
5-aminosalicylate (5-ASA) preparations as a first-line medication. Non-responders may receive cytapheresis (CAP) as monotherapy. Corticosteroids or an anti-tumour necrosis factor (TNF) biologic may be added to CAP if complete remission was not achieved with CAP monotherapy. The dose of pharmacologics may be tapered gradually or discontinued when patients achieve remission or their conditions improve.

Figure 1



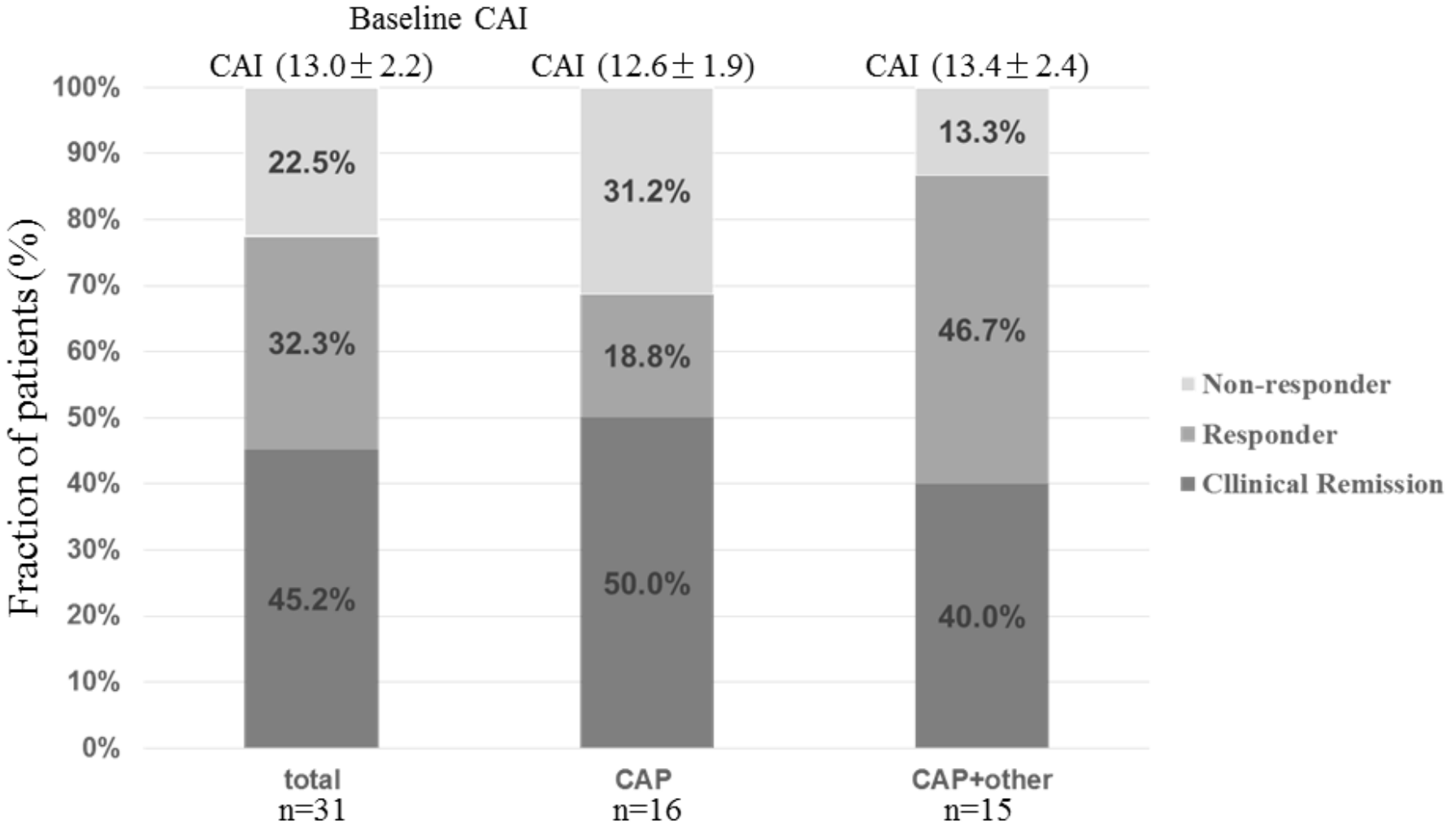
Nomura, et al. Figure 1

Figure 2



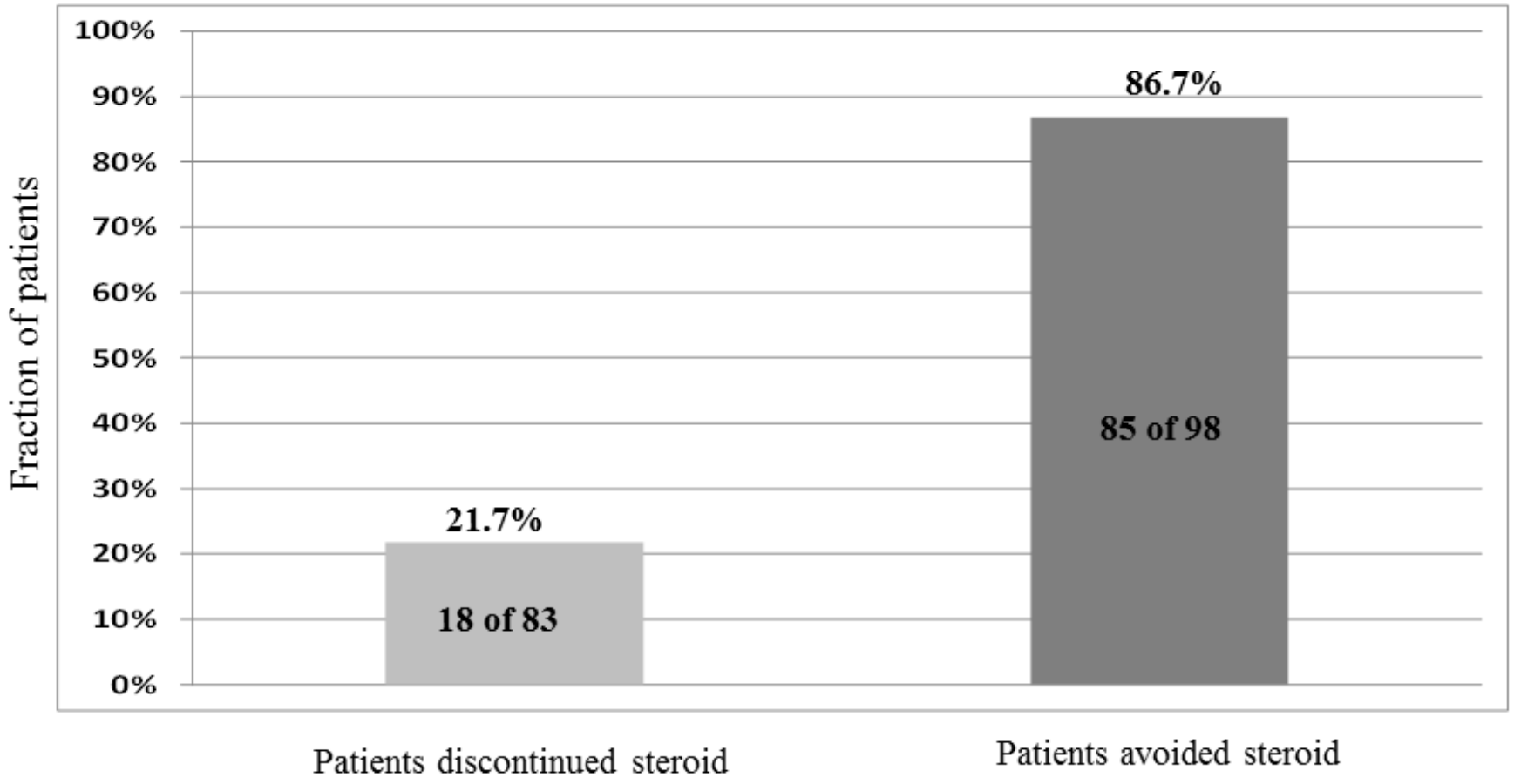
Nomura, et al. Figure 2

Figure 3



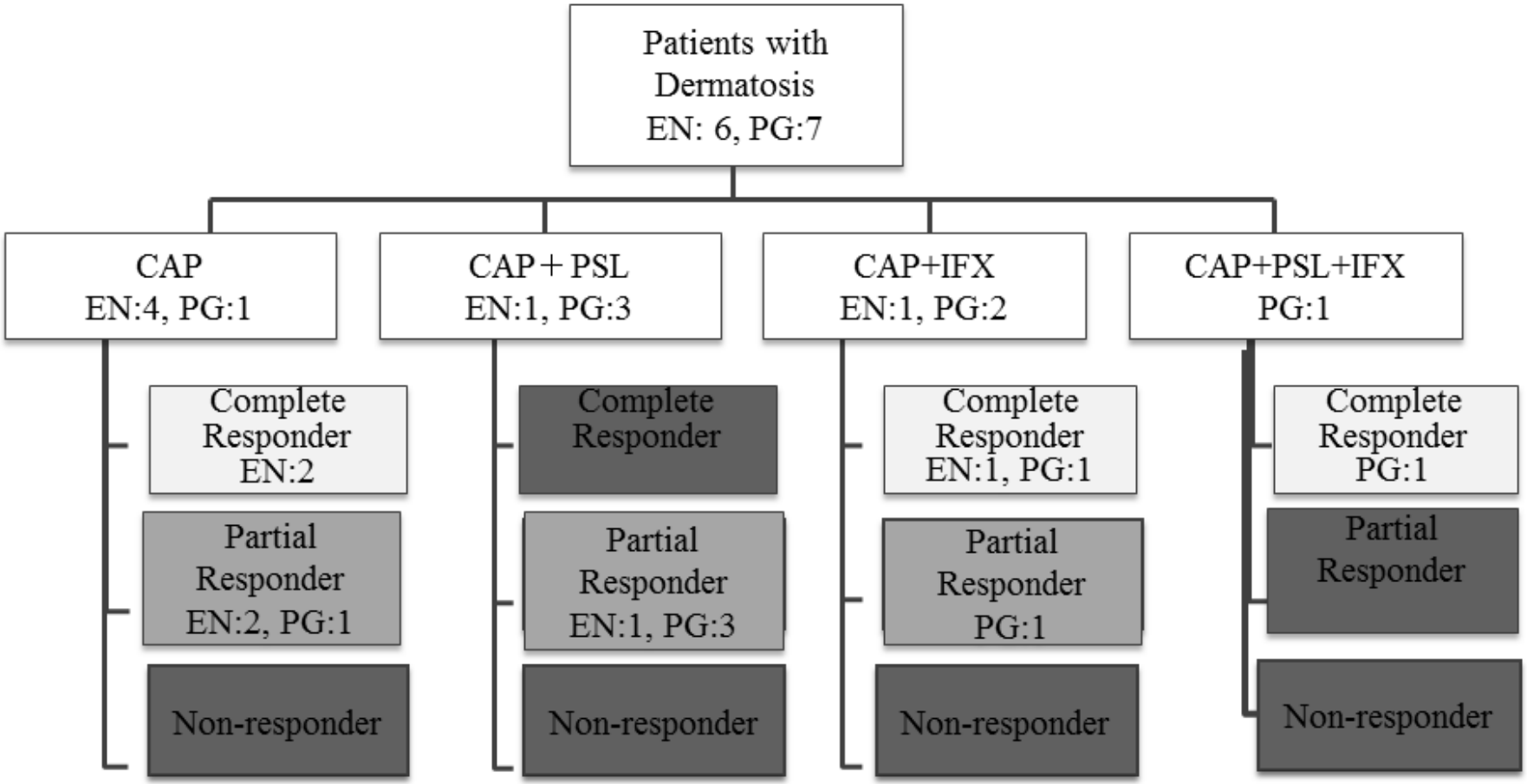
Nomura, et al. Figure 3

Figure 4



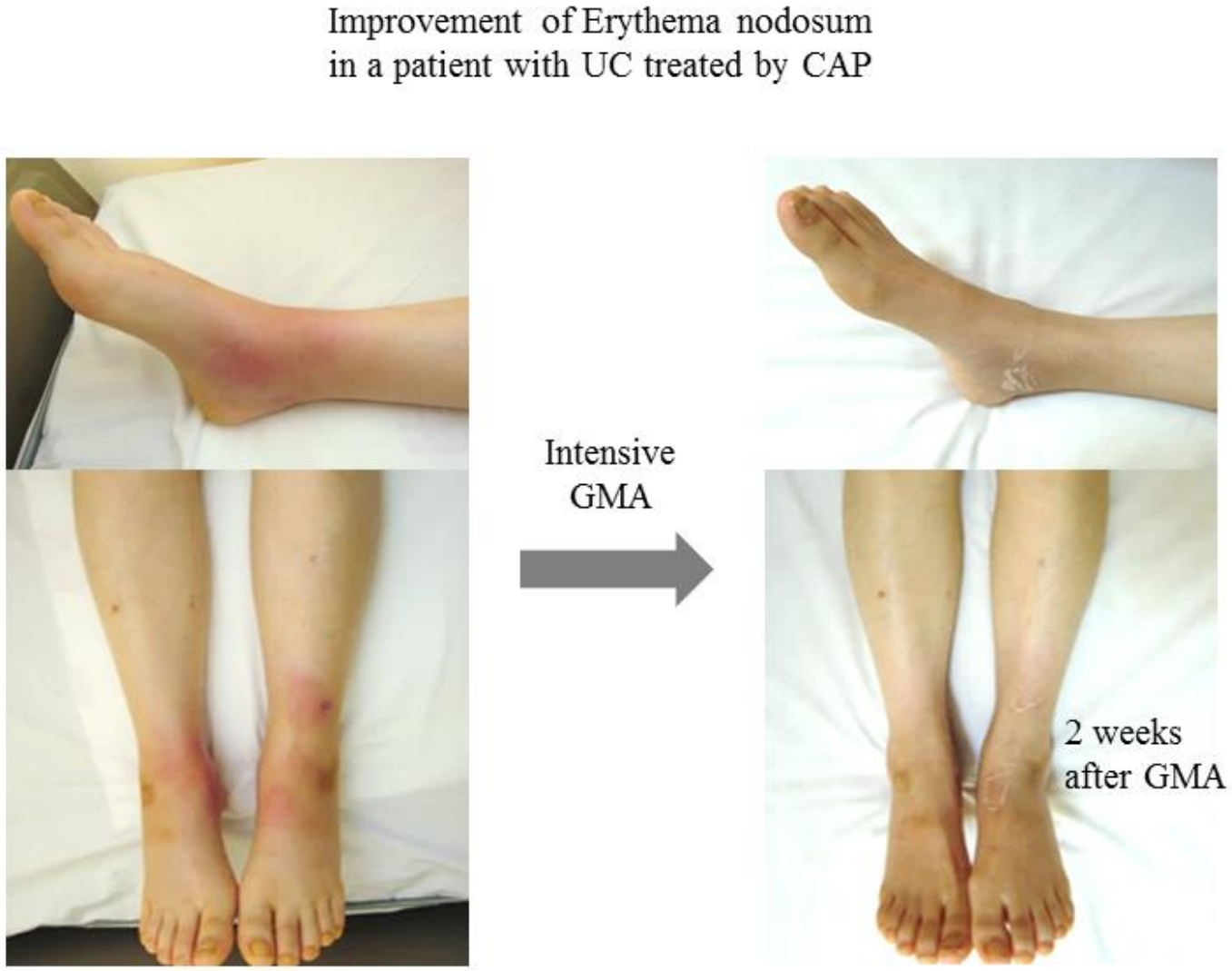
Nomura, et al. Figure 4

Figure 5



Nomura, et al. Figure 5

Figure 6

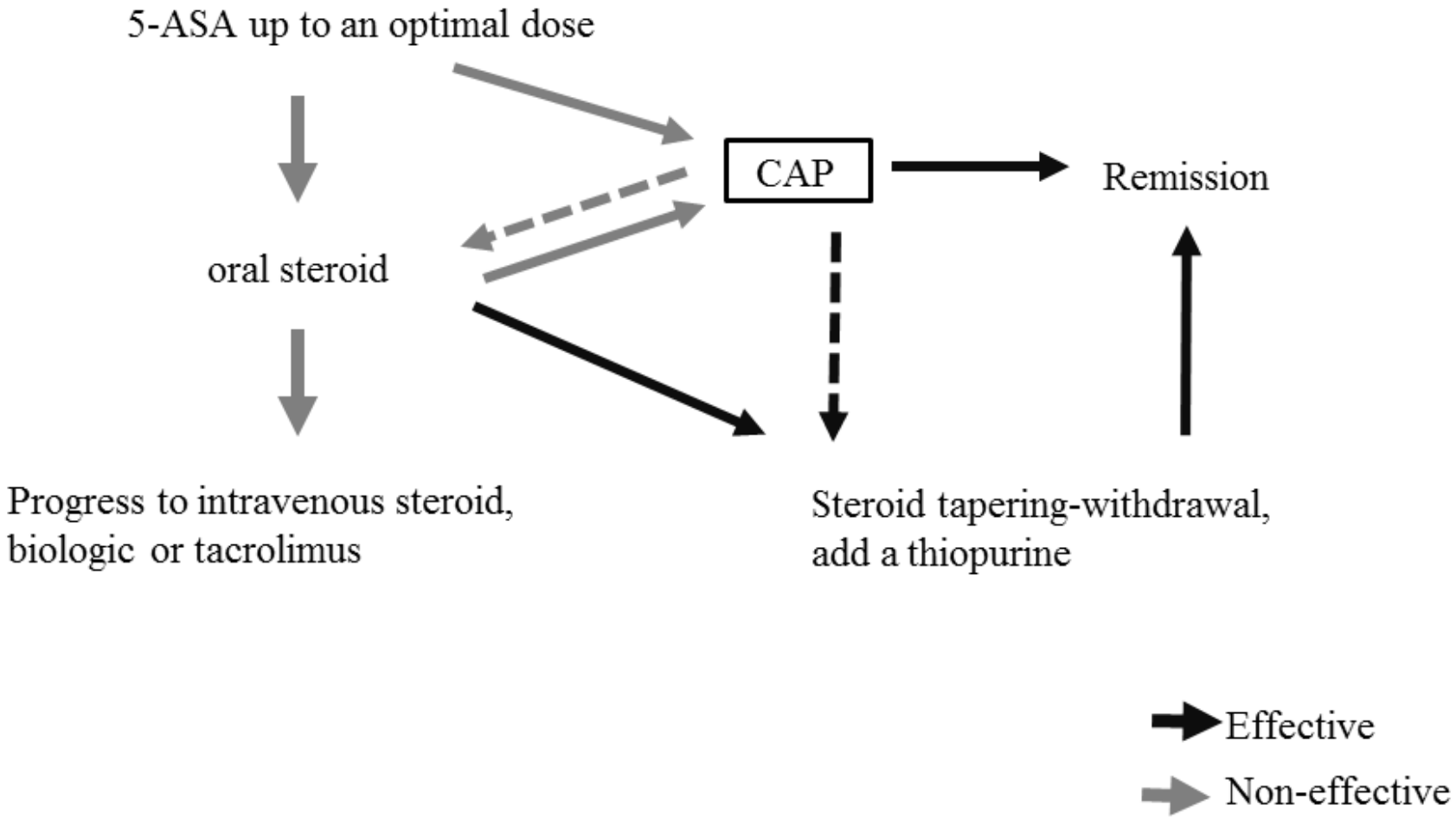


Skin lesions before and after CAP.

Nomura, et al. Figure 6.

Figure 7

Patients with moderate to severe UC, together with skin lesions as extra-intestinal manifestations



Nomura, et al. Figure 7

Table 1. Baseline demographic variables of the 181 patients included in this retrospective investigation

Age, yr (range)	38.3 (17-65)
Gender (Male/Female)	78/103
Extent of UC (Total/Left sided colitis/Proctitis)	114/55/12
Severity of UC (Mild to Moderate/Sever)	122/59
Clinical activity index, CAI (range)	9.4 (5-19)
Concomitant medication (n=103)	Prednisolone only: 79 Prednisolone + Infliximab or Tacrolimus: 14 Infliximab or Tacrolimus: 10

When appropriate, average data and ranges are presented.