Topical Treatment with the Toll-like Receptor Agonist DIMS0150 Has Potential for Lasting Relief of Symptoms in Patients with Chronic Active Ulcerative Colitis by Restoring Glucocorticoid Sensitivity

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Background: Patients with chronic active ulcerative colitis (UC) are regarded as treatment failures and represent an area of high unmet medical need, as normally the only remaining option is colectomy.

Methods: We treated a total of eight chronic active severe UC outpatients with the immunomodulatory agent DIMS0150 as an add-on to current therapies. Seven patients received a single topical dose of 30 mg and one special case subject received three doses with 4 weeks between dosing occasions. All patients were classed as treatment failures and were elected for colectomy. Efficacy evaluation was determined in terms of colitis activity index, endoscopic improvement, and histologic disease activity assessed primarily at week 12 with a follow-up period of over 2 years. Glucocorticoid sensitivity was assayed by in vitro measurement of interleukin 6.

Results: All patients demonstrated a pronounced and rapid reduction in their colitis activity index within 1 week following a single intracolonic administration via colonoscope of the agent DIMS0150. Further improvements were evident at week 4, resulting in a clinical response rate for the single-dose treatment of 71%, with 43% in clinical remission. By week 12 the clinical response and remission rates had reached 82% and 71%, respectively. A follow-up period of over 2 years posttreatment indicated that all but one of the treated patients had avoided the need for colectomy, with the longest patient being in symptom-free remission for over 27 months. Treatment with DIMS0150 restored glucocorticoid sensitivity.

Conclusions: DIMS0150 may have the potential to be an effective agent to treat chronic active UC patients with the prospect to avoid colectomy on a long-term basis and is currently the subject of a clinical phase III study (EudraCT number: 2011-003130-14).

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Key Words: ulcerative colitis, Toll-like receptor agonist, DIMS0150, steroid resistance, colectomy

While our understanding of the etiology of ulcerative colitis (UC) has grown over the years, the picture emerging is one of a complex interplay between genetic,[1,2] microbial,[3] and environmental factors[4] as well as intestinal epithelial function[5] and the mucosal immune system.[6] What is also apparent is that no factor alone appears to be sufficient to trigger the development of the disease and the contribution of each individual component may vary between patients.[7] The clinical presentation of UC depends on the extent and severity of the disease; however, predominant features include blood in stool, bowel frequency, passage of mucopus, and abdominal pain and tenesmi.[8]

Effective clinical management of active UC requires a comprehensive understanding of the disease extent, the severity as well as the potential risks and benefits of the available interventions, with a focus on induction and maintenance of remission. Corticosteroids remain the cornerstone of initial therapy, yet a third of patients will fail to respond[9] and further management involves critical and timely decisions on whether to use rescue therapy in the form of immunomodulatory drugs such as cyclosporine A or anti-tumor necrosis factor (TNF) therapies such as infliximab.[10] Current data suggest that rescue with cyclosporine A and infliximab are efficacious in the short- to medium-term perspective[11,12] but the long-term outcome seems less favorable.[13] Furthermore, a significant proportion of UC patients will have recurrent flares or chronic continuous

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disease despite receiving conventional symptomatic treatment, and within a 10-year period some 20% of these patients will require surgical intervention.[14]

New understanding of the underlying pathogenesis of UC has spurred the development of new biological therapeutics,[15] and continued use of conventional therapies has allowed optimization strategies to be designed and tested under appropriate clinical settings.[16]

The synthetic DNA-based immunomodulatory sequence 0150 (DIMS0150) is a first in class compound under clinical development for severe, chronic active, treatment-refractory UC. It functions as an immunomodulator and induces the activation of the Toll-like receptor 9 (TLR9) pathway in effector cells such as T and B lymphocytes, dendritic cells, and macrophages.[17] These cells reside in abundance on mucosal surfaces.[18] TLRs play an essential role in the perception of pathogens and shape the complex host immunological responses that occur during infection.[19,20] Prior in vitro and in vivo studies (data not published) designed to elucidate the mode of action of DIMS0150 suggest the compound is capable of restoring a subject's sensitivity to glucocorticoids through activation of the TLR9 receptor. Activation results in the production of specific cytokines such as IL-10 and type I interferons from human peripheral blood mononuclear cells (PBMCs). Theses cytokines have been demonstrated to increase steroid sensitivity in cells derived from steroid-resistant UC patients[21] and human monocytes.[22] Local colonic administration of DIMS0150 in steroid-refractory UC subjects places the agent in direct contact with an abundance of target cells harboring the TLR9 receptor. Upon activation, these cells produce steroid-sensitizing cytokines which, in addition to inducing a local sensitizing effect, are able to enter the systemic circulation and induce a peripheral steroid-sensitizing effect. This appears to be more likely than a direct systemic response to DIMS0150 which, with a molecular size of around 6000 Da, is not able to enter the general circulation following colonic administration. Indeed, there is little evidence to support systemic exposure following colonic delivery. The lack of systemic exposure may also underlie the favorable safety profile observed in preclinical and clinical studies with DIMS0150 (data not published).

We report here the use of DIMS0150 as add-on therapy for the treatment of chronic active UC patients on concomitant glucocorticoid therapies as presented by an uncontrolled, prospective treatment series comprised of eight patients.

MATERIALS AND METHODS

Patients

Over the course of 2½ years eight chronic active UC outpatients were treated with DIMS0150 as an add-on to their current therapies, with one special case subject receiving three doses of DIMS0150 with 4 weeks between dosing occasions. A diagnosis of UC was established based on clinical, endoscopic, and histological features. Written consent was received for all patients and the treatment approved by the relevant local Ethics Committees.

All patients were considered for elective colectomy based on the treating physician and surgeon's assessment. All were judged as being treatment failures with a documented history of not responding adequately to effective dosing regimes of available treatments including high-dose intravenous glucocorticoids. Additionally, all patients had previously received two applications of infliximab at 5 mg/kg with 2 weeks between dosing occasions but completely failed to show any response. As this apparent lack of response occurred at the initiation of infliximab treatment, it was reasoned that it was related to low or missing efficacy rather than due to the induction of antibodies. Due to the persistent severe condition of the disease, further treatment with infliximab was not recommended, as this would have required patients to endure their condition for an additional 4 weeks according to the infliximab induction scheme. As a result, all patients were offered DIMS0150 treatment instead.

All subjects were on a stable and tolerable dose of glucocorticoid medication; baseline characteristics are given in Table 1. Subjects who were deemed likely to require prompt clinical intervention or cases of expected colectomy were not considered.

Efficacy Evaluations

The suitability of DIMS0150 as a potential rescue therapy to prevent colectomy, on a mid-term basis of 6 months, if colectomy was elected as the preferred treatment option, was evaluated. Other objectives addressed response (a decrease in Clinical Activity Index [CAI] score by $\geq$5 units from baseline) or remission (CAI score of $\leq$4 points) and the prevention of colectomy on a long-term basis of more than 6 months.

Endoscopy was assessed according to the Rachmilewitz composed activity index[23] scale (0–12) where complete endoscopic remission is represented by 0–3. Histological assessments were made in accordance with the Geboes[24] scale (0–5) where likewise complete resolution is indicated by a score of zero. Complete clinical remission was defined as a CAI score of 0 or 1, with a concomitant endoscopic score of 0–3. Clinical assessment of all efficacy parameters were made at weeks 1, 4, and 12 for those subjects receiving a single dose of DIMS0150 and additionally at weeks 8, 26, 28, and 36 for the multidosed subject. Those patients who received additional dose(s) of DIMS1050 due to a relapse of symptoms were likewise evaluated at weeks 1, 4, and 12. For all visit occasions, adverse events were recorded.

Safety

On no occasion were any adverse events recorded in relation to treatment with DIMS0150.

TABLE 1. Baseline Characteristics of the Patients

Patient	Age	Sex	Disease Duration	Disease Extent	Treatment History		Current Medication
					Refractory to Prednisolone	Refractory to Infliximab therapy	
p1[a]	22	Male	6 years	Pancolitis	40 mg/d	700 mg	Prednisolone 20 mg/day, S-Ompeprazol 20 mg/day
p2	44	Male	20 years	Colitis of rest colon after hemicolectomy (ano-50 cm)	40 mg/d	1000 mg	Prednisolone 40 mg/day, 5-ASA 4 g/day
p3[b]	68	Male	1 year	Ulcerative colitis (ano-80 cm)	70 mg/d	none	Prednisolone 30 mg/day, 5-ASA 4.5 g/day
p4	45	Male	4 years	Pancolitis	40 mg/d	300 mg	Prednisolone 35 mg/day, 5-ASA 3 g/day
p5[c]	46	Female	29 years	Ulcerative colitis (ano-80 cm)	30 mg/d	none	Prednisolone 10 mg/day, Azathioprine 125 mg/day
p6	27	Male	4 years	Ulcerative colitis (ano-60 cm)	20 mg/d	400 mg	Prednisolone 20 mg/day, Azathioprine 150 mg/day, 5-ASA 4 g/day
p7[c]	46	Female	25 years	Proctosigmoiditis	100 mg/d	none	Prednisolone 10 mg/day, Azathioprine 100 mg/day
p8	50	Male	5 years	Pancolitis	100 mg/d	500 mg	Prednisolone 25 mg/day

[a]Patient also showed no response to treatment with 80 mg adalimumab.
[b]Patient has sinus brachycardia and diabetes mellitus type II and had a posterial myocardial infarct; not eligible for anti-TNF treatment.
[c]Patient refused to take infliximab.

Treatment

Seven of the eight selected patients received a single intracolonic dose of 30 mg of DIMS0150 diluted in 50 mL of sterile water in addition to their current treatments. Application of the drug was performed during colonoscopy with the aid of a spraying catheter inserted through the colonoscopy's biopsy channel and delivered approximately to the upper portion of the descending colon or to the transverse region. In instances of a relapse (as determined by a deterioration of the disease of $\geq$4 CAI units) an additional dose(s) of DIMS0150 was offered and the patient subsequently followed.

One special case patient received three doses of DIMS0150 at 4-week intervals and blood samples were obtained prior to each treatment. PBMCs derived from these blood samples were subsequently analyzed for steroid sensitivity. Table 2 outlines patient clinical response parameters at weeks 1, 4, and 12 and time of additional dose(s) in those subjects who experienced a relapse.

TABLE 2. Disease Activity Overview of Patients p1-p7

Patient	Disease Activity at Dosing			Disease Activity at 1 Week			Disease Activity at 4 Weeks			Disease Activity at 12 Weeks			Additional DIMS0150 Dose(s)	Follow-up (Months)
	CAI	Endo	Histo	CAI	Endo	Histo	CAI	Endo	Histo	CAI	Endo	Histo		
p1	10	10	4/5/5	8	8	4/5/5	0	5	4/5/5	4	4	3/5/5	6 and 12 months	Colectomized after 17 months
p2	14	9	–/–/5	3	5	–/–/3	4	3	–/–/2	5	5	–/–/3	5, 10, 20, 23 and 26 months	27
p3	13	10	0/3/3	8	6	–/4/3	6	3	–/2/3	1	0	–/0/1	11 months	24
p4	12	10	5/5/5	6	5	3/3/3	4	1	3/2/2	2	1	2/1/1	16, 17 and 18 months	23
p5	11	9	0/5/4	8	7	–/1/3	6	5	–/0/1	4	4	–/0/0		18
p6	10	9	0/3/5	7	7	–/3/3	6	5	–/2/4	0	2	–/0/1		15
p7	9	5	0/0/3	7	5	–/0/3	6	5	–/0/3	6	5	–/0/3		13

Dash denotes no biopsy taken.

Determination of Steroid Sensitivity

Cell Preparation

Around 30 mL sodium heparinized blood was taken from the patient prior to each DIMS0150 dosing occasion (0 days, week 4, and week 8) and at weeks 12, 26, and 36. For control, blood samples from 10 healthy individuals were taken under prior written consent. PBMCs were separated on Ficoll-Hypaque by gradient centrifugation at 400*g* for 30 minutes at 20°C. Thereafter, the cells were harvested from the plasma/Ficoll interface and washed 3 times in phosphate-buffered saline (PBS, pH 7.4; Ca^{2+} and Mg^{2+} free). The number and viability of the cells were determined by Trypan blue exclusion. The cells were diluted to 10^7 cells/mL with RPMIc (RPMI 1640 containing 10% heat-inactivated fetal bovine serum [FBS], PeSt [100 U/mL penicillin, 100 μg/mL streptomycin], 2 mM L-glutamine, 5 μg/mL gentamycin, and 5 mM Hepes). Isolated PBMCs were cultured in 96-well culture plates (Becton Dickinson, San Jose, CA) at a concentration of 0.5×10^6 cells/well. Ficoll-Paque was purchased from Amersham Bioscience (Uppsala, Sweden); PBS, gentamycin, and FBS were purchased from Gibco-Invitrogen (La Jolla, CA), and RPMI, PeSt, glutamine, and Hepes were purchased from Sigma Aldrich (Sweden).

In Vitro Stimulation

Immediately after plating, cells were stimulated with lipopolysaccharide (LPS) (100 pg/mL) (InvivoGen, San Diego, CA) in the presence or absence of Dexamethasone (Sigma Aldrich) (10^{-6}, 10^{-8}, or 10^{-10} M). RPMIc medium alone served as a negative control. Cells were incubated in a humidified SteriCycle CO2 cell culture incubator (Thermo Forma Steri-Cycle, Marietta, OH) at 5% CO_2 in air at 37°C for 48 hours. Cell supernatants were then harvested to measure their cytokine content.

Detection of Secreted Cytokines

Interleukin 6 (IL-6) was measured by cytometric bead array (CBA) (Becton Dickinson Biosciences, Heidelberg, Germany) Flex kit according to the manufacturer's protocol on a FACSArray flow cytometer followed by analysis using FCAP Array software (BD Biosciences). The lower detection limit was 20 pg/mL for IL-6 cytokine.

Ethical Considerations

Ethical approval for the treatment of patients with DIMS0150 was granted by the local ethics authority and performed with written consent by the participating patients. For the one subject receiving three consecutive doses of DIMS0150, blood was taken prior to each dose with written consent from the subject.

RESULTS

Efficacy After a Single Dose

After treatment with DIMS0150, 43% (3/7) of patients demonstrated a clinical response at week 1, with one case of clinical remission. By week 4, 71% (5/7) of patients had a clinical response and 43% (3/7) were in remission. At week 12 clinical response and remission rates were 86% (6/7) and 71% (5/7), respectively, with two cases of complete clinical remission. Figure 1a illustrates the individual CAI scores of the patients up to 12 weeks postdosing and Figure 1b shows the median CAI score in the same period.

Endoscopic evaluation at week 1 showed that 86% (6/7) had a decrease in their endoscopic index of $\geq$2 units from baseline, with one subject (p4) recording a decrease of five units. At week 4, two patients (p3 and p4) were in endoscopic remission and four of the remaining five patients had a baseline improvement of $\geq$4 units or more. By week 12, 43% (3/7) of patients were in complete endoscopic remission, with further improvement noted for four of the remaining five patients (Table 3). Figure 2a,b provides individual and median endoscopic scores across the 12-week period, respectively. For histological evaluation, three biopsy specimens representing three colonic regions (ascending, transverse, and descending) were taken from the same area at baseline and after treatment and the scores are given in Table 2. Overall, there was a marked improvement in histological scores at week 12 in over 50% (4/7) of subjects with a decrease of at least $\geq$2 units from baseline. Improvements were also reflected in the extent of the disease, with three patients experiencing reduced colonic involvement.

Four patients (p1–p4) were given additional doses of DIMS0150 due to a relapse of symptoms at the times indicated (Table 2), the first of these occurring 5 months after the initial dose. All subjects had an improvement in their CAI scores following further treatment with DIMS0150. As a result of responding to DIMS0150, all, with the exception of one patient, have so far avoided the need for colectomy, with the longest period currently being around 27 months (Fig. 3). Despite the initial response to DIMS0150, patient (p1) decided to undergo colectomy following a relapse some 17 months after the first treatment.

All subjects were on a stable and tolerable dose of prednisolone at the time of dosing (baseline) ranging from 10–40 mg/day. Following DIMS0150 treatment the median daily prednisolone dose had been reduced from 20 mg/day to 10 mg/day by week 12, with one subject discontinuing use (Table 4).

Efficacy After Multiple Doses

For the special case patient (p8) we administered three doses of 30 mg DIMS0150 as an add-on to current therapies with 4-week intervals between dosing. In addition to monitoring clinical response, endoscopic, and histological parameters (Table 3), we obtained blood samples immediately prior to each dosing occasion and again at weeks 12, 26, and 36 with the intention of monitoring the patient's steroid sensitivity. Following treatment, the

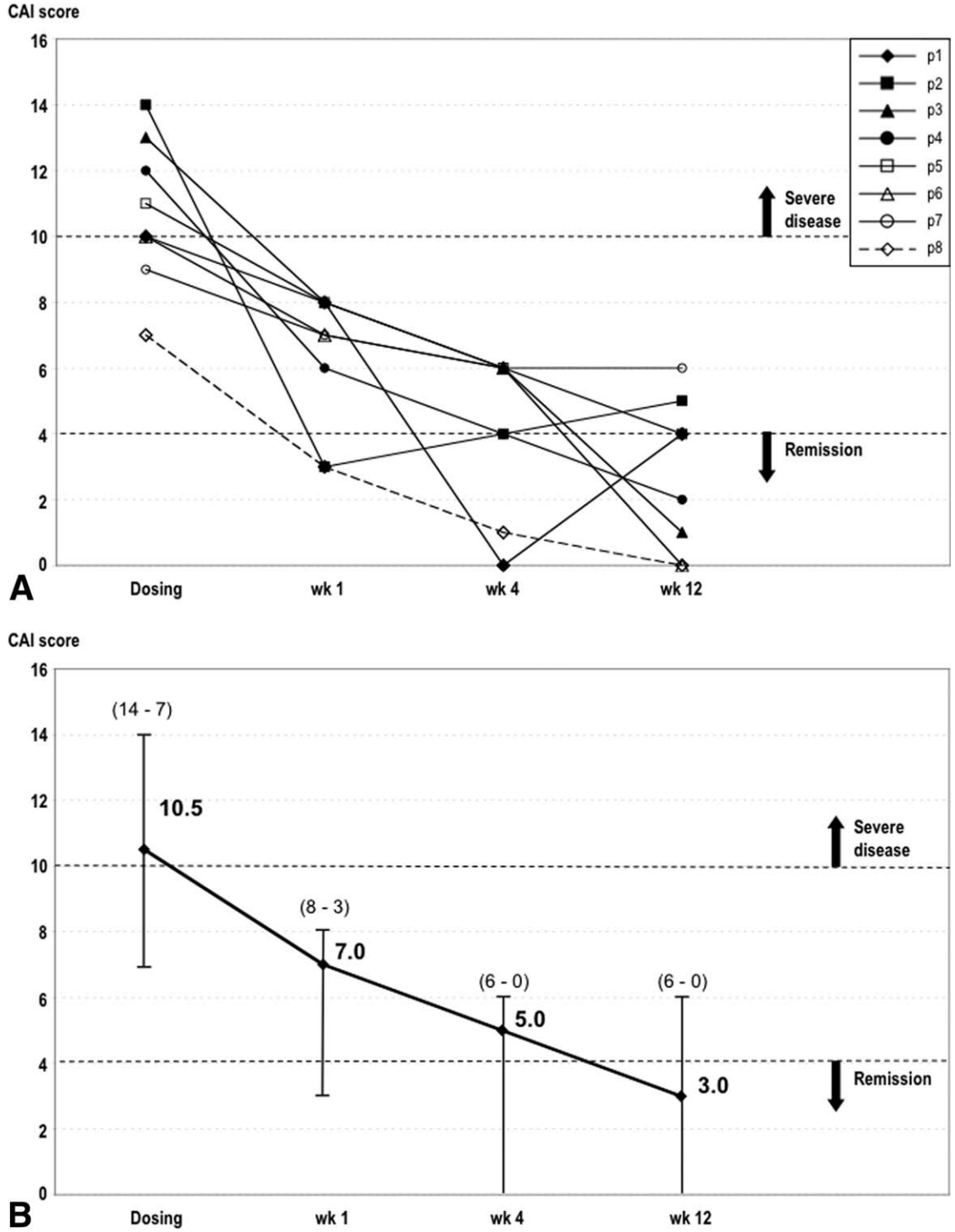

FIGURE 1. (a) Change over time in CAI score from baseline of the individual patients following single-dose DIMS0150 treatment. Note: dotted line indicates special case subject who received three doses of DIMS0150. (b) Median change in CAI score (bold values) following single-dose DIMS0150 treatment. Vertical bars depict range of CAI scores.

subject was in complete remission at week 8; however, experiencing a slight worsening of symptoms by week 26 (Fig. 4). Our previous work suggests that DIMS0150 functions as a glucocorticoid resensitizer and we wanted to determine whether treatment with DIMS0150 had restored the patient's glucocorticoid sensitivity. Consequently, the

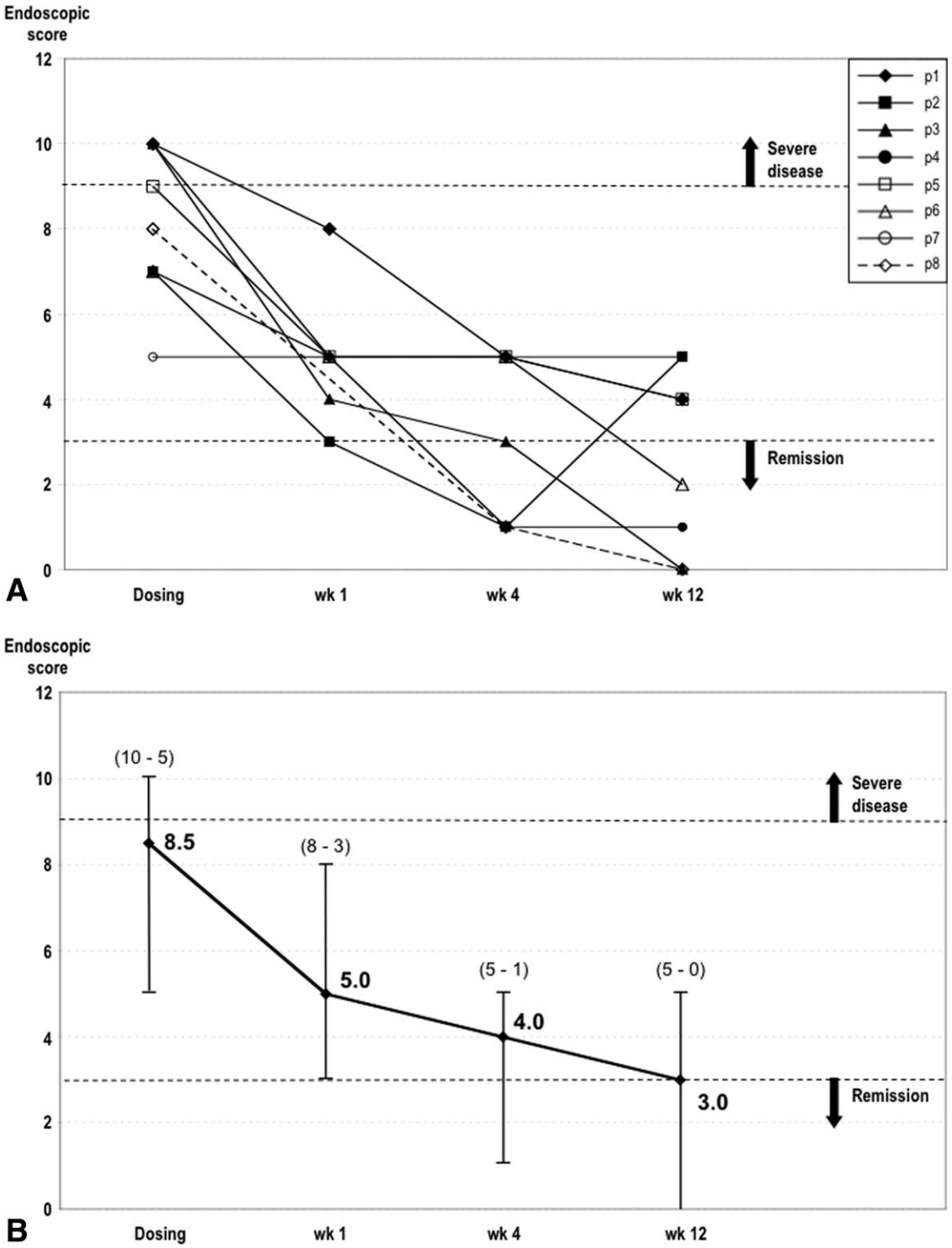

FIGURE 2. (a) Change over time in the endoscopic score from baseline of the individual patients following single-dose DIMS0150 treatment. Note: dotted line indicates special case subject who received three doses of DIMS0150. (b) Median change in endoscopic score (bold values) following single-dose DIMS0150 treatment. Vertical bars depict range of endoscopic scores.

steroid dose was increased from 10 mg to 30 mg per day at week 27 and we noted a marked improvement in the CAI score. By week 36 the patient was in complete clinical and histological remission, suggesting that the subject responded to the glucocorticoid treatment.

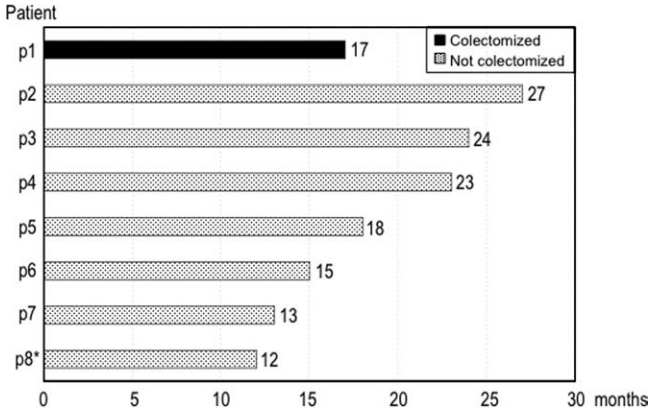

FIGURE 3. Length of colectomy-free period following DIMS treatment to March 2011. *Subject was given three doses of DIMS0150 with 4 weeks between dosing occasions.

Monitoring of Steroid Sensitivity in Response to DIMS0150 Treatment

PBMCs were isolated from the collected blood samples derived from patient (p8) and assayed in vitro for steroid sensitivity. One way to achieve this is to monitor the degree of suppression of LPS-induced IL-6.[25,26] Figure 5 demonstrates that at the time of receiving the first dose of DIMS0150, PBMCs derived from the subject failed to respond to the applied concentrations of dexamethasone as no suppression of IL-6 was seen, suggesting the subject was steroid resistant.

At week 4, just prior to the second dose of DIMS0150, there was a marked suppression in levels of IL-6 seen with the highest concentration of dexamethasone, indicating a partial response of the subject's PBMCs. By week 8 and just prior to the last dose of DIMS0150, further steroid sensitivity was gained, in that both of the two highest concentrations of dexamethasone could repress IL-6. By week 12, derived PBMCs demonstrated steroid sensitivity levels of normal to better than normal, in that all three concentrations were effective at reducing the levels of induced IL-6, indicating that the subject's steroid response had been further improved. These findings correlated with the marked improvement of clinical symptoms in this subject.

Interestingly, by week 26 the lowest steroid dose was no longer able to repress IL-6, indicating a potentially reduced steroid sensitivity. However, this level of sensitivity was still evidently sufficient for the marked improvement observed in the patient following the increased prednisolone dose. By week 36 the patient's steroid sensitivity had decreased further, as now only the highest dose was able to repress IL-6. Collectively, the in vitro steroid sensitivity of the PBMCs derived from subject (p8) appeared to correlate well with the clinical outcome following DIMS0150 treatment, and supports the findings of Hearing et al,[27] who demonstrated that in vitro lymphocyte steroid resistance is correlated with outcome in steroid-treated severe UC.

TABLE 4. Concomitant Steroid (Prednisolone) Usage at Baseline and After Treatment

Patient	At Dosing	Week 1	Week 4	Week 12
p1	20 mg/day	20 mg/day	20 mg/day	10 mg/day
p2	40 mg/day	40 mg/day	30 mg/day	12.5 mg/day
p3	15 mg/day	15 mg/day	10 mg/day	Steroid free
p4	35 mg/day	35 mg/day	20 mg/day	5 mg/day
p5	10 mg/day	10 mg/day	10 mg/day	10 mg/day
p6	20 mg/day	20 mg/day	20 mg/day	10 mg/day
p7	10 mg/day	10 mg/day	10 mg/day	10 mg/day
p8	25 mg/day	25 mg/day	25 mg/day	20 mg/day

DISCUSSION

Total proctocolectomy is typically the procedure of choice for debilitated patients with acute, medically refractory UC.[28] While surgical intervention may be curative and provide a better quality of life,[29] it is not without

TABLE 3. Disease Activity Overview of Patient Receiving 3 Doses of DIMS0150

	Disease Activity at Dosing			Disease Activity at 1 Week			Disease Activity at 4 Weeks			Disease Activity at 8 Weeks		
Patient	CAI	Endo	Histo	CAI	Endo	Histo	CAI	Endo	Histo	CAI	Endo	Histo
p8	7	8	5/5/5	3	n.d.	n.d.	1	1	2/2/2	0	0	0/0/0
	Disease Activity at 12 Weeks			Disease Activity at 26 Weeks			Disease Activity at 28 Weeks			Disease Activity at 36 Weeks		
Patient	CAI	Endo	Histo	CAI	Endo	Histo	CAI	Endo	Histo	CAI	Endo	Histo
p8	0	0	0/0/0	4	n.d.	n.d.	1	n.d.	n.d.	1	0	0/0/0

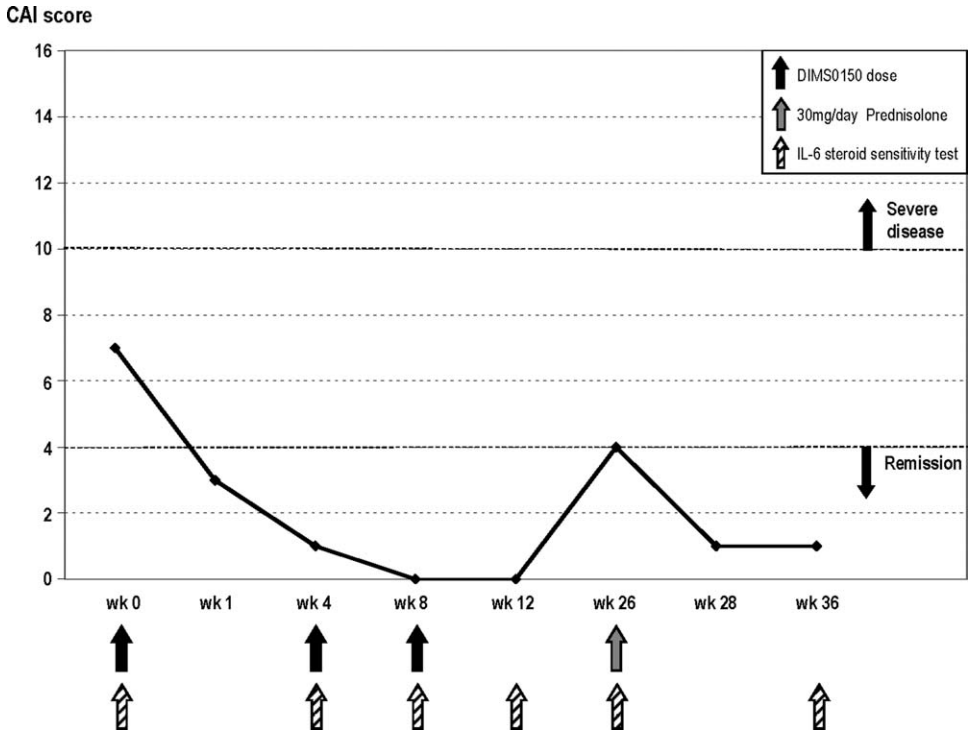

FIGURE 4. Patient (p8) CAI response following three doses of DIMS0150 as indicated. Hatched arrows indicate time of blood sample collection to evaluate the steroid sensitivity status of the patient. Solid gray arrow indicates the timepoint at which the steroid dose was increased.

considerable risks to the patient[30] and the procedure itself presents a significant pre- and postoperative morbidity as well was a substantial economic burden to the healthcare system.[31] Consequently, the need for alternative treatments is evident.

The results from the present case series indicate that topical administration of the immunomodulatory agent DIMS0150 may have the potential to induce a clinical response in this particular group of refractory UC patients. For those seven cases that received a single treatment of

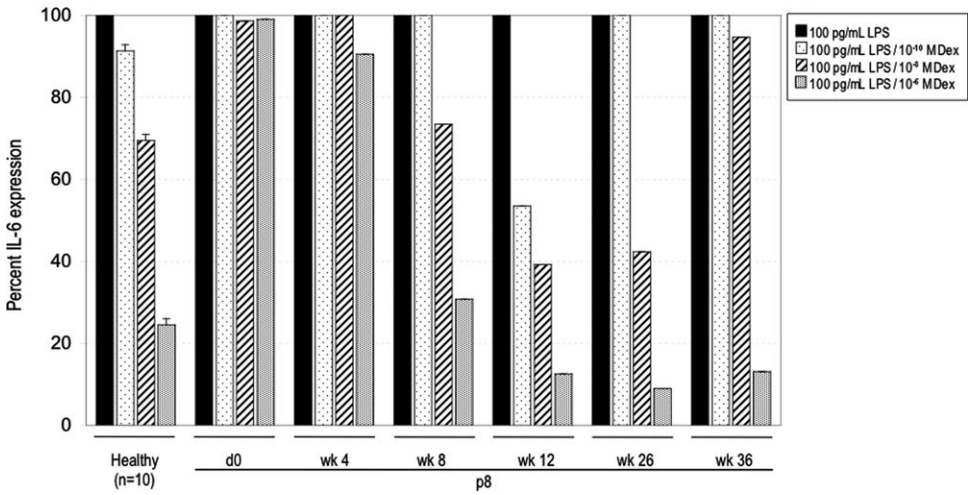

FIGURE 5. Steroid sensitivity analysis of PBMCs derived from the special case patient (p8) at the indicated timepoints. Derived PBMCs were stimulated for 48 hours with LPS in the presence or absence of three concentrations of dexamethasone and levels of IL-6 measured using a FACSArray flow cytometer. Blood samples derived from healthy controls with written consent were used to determine the level of suppression in steroid-sensitive subjects.

DIMS0150, 71% (5/7) were in clinical remission, with 43% having complete resolution of endoscopic involvement at week 12. Equally, there was a marked improvement in histological scores, with over 50% of patients demonstrating a reduced score of at least two units from baseline. These findings are important, as achievement of mucosal healing has been associated with better outcome, less surgery, and less hospitalization.[32,33] No adverse events were recorded following DIMS0150 treatment, reflecting both our previous clinical experiences of DIMS0150 in over 160 patients and the lack of any significant toxicological findings in both rodent and primate studies.

From the perspective of subjects with intractable UC having chronic, continuous symptoms we observed that treatment with single or multiple doses of DIMS0150 circumvented the need for colectomy in 87% (7/8) of patients, and for some subjects this has meant the return to a more normal quality of life. Induction of sustained remission also has other important implications, as patients with longstanding UC have an increased risk of colorectal cancer.[34,35]

The subanalysis of patient case (p8) in this report has provided further evidence to support the hypothesis that DIMS0150 functions by imparting a clinical response to glucocorticoids by restoring sensitivity. We have been able to document a shift in the steroid sensitivity status of the patient's PBMCs following three doses of DIMS0150 from one of steroid-resistance to one of steroid-sensitivity by week 12, with the subject being in complete remission. There was a good correlation between clinical response and increased steroid sensitivity to the three concentrations of dexamethasone used. Collectively, the response to dexamethasone indicates a gradual increase in steroid sensitivity in the subjects' PBMCs to the applied steroid concentrations up until week 12. Thereafter there was a progressive decrease in response up to week 36, suggesting a likely return to previous resistant levels. This could be indicative of a potential future relapse despite the subject being in complete remission at the time and that additional treatment of DIMS0150 may be needed to maintain a status of steroid sensitivity.

The observation of improved steroid sensitivity of the subjects derived PBMCs following local DIMS0150 treatment would appear to suggest more than a local action of DIMS0150. Administration of DIMS0150 on colonic mucosa restored steroid sensitivity of peripherally derived PBMCs, indicating a systemic sensitization effect to steroids. This may equally offer an explanation regarding previous clinical observations where the extent of disease appeared not to be an important factor regarding where DIMS0150 was locally administered, as subjects with pancolitis responded equally well as those with just left-sided involvement. The median daily dose of prednisolone following DIMS0150 treatment decreased to 10 mg/day, with one subject achieving steroid-free remission by week 12. Weaning of prednisolone dosage was initiated at week 4, where most DIMS0150-treated subjects had demonstrated a substantial reduction in their CAI scores and the risk of potentially inducing a relapse could be minimized. Tapering of prednisolone dosage was performed on an individual basis according to the physician's judgment and not to a uniform scheme. The intention was to determine whether it was possible to reduce steroid usage without exacerbating the condition. While a fixed tapering scheme may be appropriate for some patients, a more individual approach was favored. Steroid-free remission is clearly a desirable endpoint and most subjects had reduced daily prednisolone doses at week 12, concomitant with improved CAI scores.

Restoring a patient's sensitivity to glucocorticoids is a valuable option, as they still remain one the most efficacious antiinflammatory agents and are the mainstay therapy for moderate to severe attacks of UC.[36] No other class of medication acts as rapidly and with such consistent results to control disease activity, improve patient symptoms and in UC, promote endoscopic and histological improvement.[37] Furthermore, the need for other immunomodulatory agents such as cyclosporine,[38] where the long-term risks/benefits are not clear,[39] could be reduced. Moreover, there are concerns regarding sequential treatment of UC patients with various immunomodulatory biologics due to the risk that such patients may progress to complicated and difficult to treat cases of UC where colectomy, in this setting, is inevitable and carries a higher risk of mortality.[40] It is possible that the clinical threshold for elective colectomy in subjects with inflammatory bowel disease may be too high[41] and the threshold criteria and optimal timing of elective surgery should be carefully evaluated.

In conclusion, the collection of case series presented illustrates the potential usefulness of DIMS0150 to induce clinical remission in cases of steroid-refractory elective colectomy patients with the prospect to reduce the need for colectomy on a long-term basis. While DIMS0150 may offer a much-needed alternative treatment option, its true clinical benefit is currently the focus of an ongoing phase III clinical study.

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