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Adalimumab for Ocular Inflammation

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Abstract

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For a complete roster of members of Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Research Group, see the Appendix.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

The author(s) have made the following disclosure (s): John H. Kempen: (consultant) Lux Biosciences, (consultant) Allergan, (consultant) Alcon, (consultant) Can-Fite, (consultant) Clearside, (consultant) Sanofi-Pasteur, (consultant) Xoma; James Rosenbaum: (equity owner) Amgen, (consultant) Abbott, (consultant), ESBATech, (consultant) Lux Biosciences, (consultant) Centocor, (consultant) Genentech; Douglas A. Jabs: (consultant) Roche; (consultant) Genzyme Corporation; (consultant) Novartis; (consultant) Allergan; (consultant) Glaxo Smith Kline; (consultant) Applied Genetic Technologies Corporation; (consultant) The Emmes Corporation; (consultant) The Johns Hopkins Dana Center for Preventive Ophthalmology; C. Stephen Foster: (consultant) Aldeyra Therapeutics, (consultant) Bausch & Lomb Surgical, (consultant) Eyegate Pharma, (consultant) Novartis, (consultant) pSivida, and (consultant) Xoma.

Purpose—To evaluate adalimumab as an immunomodulatory treatment for non-infectious ocular inflammatory diseases.

Methods—Characteristics of patients treated with adalimumab were abstracted in a standardized chart review. Main outcomes measured were control of inflammation, corticosteroid-sparing effect, and visual acuity.

Results—In total, 32 patients with ocular inflammation were treated with adalimumab. The most common ophthalmic diagnoses were anterior uveitis, occurring in 15 patients (47%), and scleritis, occurring in 9 patients (28%). At 6 months of therapy, among 15 eyes with active inflammation, 7 (47%) became completely inactive, and oral prednisone was reduced to ≤10 mg/day in 2 of 4 patients (50%). On average, visual acuity decreased by 0.13 lines during the first 6 months of treatment. Adalimumab was discontinued because of lack of effectiveness in four patients within 6 months.

Conclusions—Adalimumab was moderately effective in controlling inflammation in a group of highly pre-treated cases of ocular inflammatory disease.

Keywords

Adalimumab; Humira; ocular inflammatory disease; scleritis; TNF-α antibody; uveitis

The cytokine TNF-α participates in the pathogenesis of autoimmune ocular inflammatory diseases and belongs to a large group of signaling cytokines with functions in inflammation and apoptosis.[1] Large amounts of TNF-α are released in response to lipopolysaccharide (LPS), other bacterial products, and interleukin-1 (IL-1) release by macrophages and retinal cells (including the retinal pigment epithelium).[2] The receptors TNFR-1 (or p55) and TNFR-2 (or p75) are the targets of TNF-α and mediate its biologic activity in cells and cell membranes. TNFR-1 may be involved in pro-apoptotic and inflammatory signaling pathways, whereas TNFR-2 may be involved in cell growth and proliferation.[3]

Adalimumab (Humira®, AbbVie, Chicago, IL) is a fully human monoclonal IgG1 TNF-α antibody (mAb) approved by Food and Drug Administration as a subcutaneously administered treatment for rheumatoid arthritis, chronic plaque psoriasis and psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and juvenile idiopathic arthritis (JIA). It has been demonstrated that binding of adalimumab with surface TNF-α, results in lysis of TNF-α expressing cells *in vitro* in the presence of complement.[4]

Adalimumab has been used off-label for a wide variety of adult and childhood inflammatory eye diseases. It has been successfully used in patients with uveitis secondary to juvenile idiopathic arthritis, ankylosing spondylitis, and refractory uveitis of diverse etiologies, such as Behçet's disease, sarcoidosis, Vogt–Koyanagi–Harada disease, birdshot chorioretinopathy, scleritis secondary to rheumatoid arthritis, and orbital pseudotumor/myositis.[5–19]

In order to evaluate the impact of adalimumab on ocular inflammatory disease, using recommended analytic methods,[20] we report, herein, outcomes of 32 patients with various ocular inflammatory diseases treated with adalimumab.

METHODS

The Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study is a multicenter cohort study, whose methods have been described previously.[21] Patients treated with adalimumab in this cohort (which has follow-up through 2007) were included in this analysis.

All data were collected by a retrospective chart review and entered on standardized data entry forms for statistical analysis. The data obtained include demographic characteristics of the patients at presentation; the diagnosis and clinical features of the ocular inflammatory disease for each patient; duration of disease and follow-up; history of previous immunosuppressive drug therapy; use of corticosteroids and immunosuppressive drugs (including adalimumab); and control of and measures of inflammation at each visit. The study was performed with the approval of the Institutional Review Boards of each study center.

Inflammatory status was categorized as ‘active’ (corresponding to findings, such as anterior chamber cells of 1+ or higher, vitreous haze of 1+ or more, or described by terms such as ‘active’, ‘worsening inflammation,’ or ‘disease progression’); or ‘inactive’ (as noted by terms such as ‘quiet’, ‘quiescent’, ‘no cells,’ and ‘no active inflammation’) for every eye at every visit based on the clinician’s documentation at each visit, as described previously.[22] Control of inflammation was defined as the absence of either active or slightly active ocular inflammation sustained for at least 28 days during treatment with adalimumab, regardless of the dose of prednisone or the use of other immunosuppressive drugs. ‘Corticosteroid-sparing success’ was evaluated based on time-to-reduction of the prednisone (or prednisone-equivalent) dose to ≤10 mg/day; ≤5 mg/day; or 0 mg with sustained control of the ocular inflammation observed over a period of at least 28 days, among those ‘at risk’ (not meeting each respective criterion for success at the outset). Adalimumab was administered at the standard dose of 40 mg subcutaneously every other week, except in two patients who received 40 mg every week. Dates of discontinuation of adalimumab and the reasons for discontinuation were noted.

Frequencies of variables were tabulated for the study population using SAS (version 8.2, Cary, NC). Time-to-event outcomes and incidence rates were calculated using survival analysis in a by-eye or by-person analysis as appropriate for the outcome of interest. The 95% confidence intervals are indicated by placing the lower and upper bound of the confidence intervals as subscripts before and after each estimate.

RESULTS

In total, 32 patients who started adalimumab during follow-up were identified, with or without topical or systemic corticosteroids or concomitant immunomodulatory therapy. The demographic and clinical characteristics of this cohort are summarized in Table 1 which describes patient characteristics. The mean age was 42 years (range: 4–74 years), and the majority were white (78.1%) and female (68.7%). Anterior uveitis was the most common diagnosis in affected eyes (46.9%), followed by scleritis (28.1%) and intermediate and

posterior/panuveitis (9.4% each), with bilateral (or alternating) disease occurring in the majority of patients (78.1%). The mean interval between diagnosis of ocular inflammation and initiation of adalimumab therapy was 6.9 years (range 0–36 years). Most patients had received either topical or systemic steroids (84.4%), and had been treated with at least one immunomodulatory agent (87.5%), prior to starting adalimumab therapy.

Table 2 summarizes treatment characteristics of the cohort receiving adalimumab therapy, and describes patient characteristics. The mean duration of treatment was 2.6 years (range: 27 days to 6.2 years). Corticosteroids by any route (topical or systemic) were used at some point during therapy in 71.9% of patients. The majority (68.8%) used at least one immunomodulatory agent in addition to adalimumab, with the plurality (46.9%) using one additional agent; 15.6% using two; and 6.3% using three or more additional immunomodulatory agents. Therapy was discontinued in 13 (40.6%) patients during follow-up, with ineffectiveness being the cause of discontinuation in 4 of the 13 (30.8%). Other reasons for discontinuation were one each of the following: skin reaction, rash, fatigue and body ache, angina, swelling of rectus muscles, retinal detachment, insurance carrier non-approval, and death from unknown cause. The reason for discontinuation was unknown in one case.

Outcomes while under treatment with adalimumab are summarized in Table 3. Because risk varied over time, the proportions at 3 and 6 months are reported here, with rates available in Table 3. Of note, in contrast to Tables 1 and 2, Table 3 summarizes outcomes by eye, and not by patient. In addition, differing numbers of eyes were ‘at risk’ for a specific outcome, in this retrospective cohort analysis, at the 3 and 6 month time points, resulting in varying denominators for each outcome. By 3 and 6 months of treatment, an improvement of anterior chamber (AC) cells by two or more grades (e.g., from 2+ to 0.5+ or from 1 + to 0) occurred in 4/6 eyes ($_{22}67\%_{93}$) and 4/5 eyes ($_{29}80\%_{98}$), respectively, for which complete data were available. In addition, after both 3 and 6 months of therapy, ‘active’ inflammation, resolved to ‘inactive’ inflammation in 7/15 eyes ($_{20}47\%_{76}$). In contrast, 6/23 of initially ‘inactive’ eyes became ‘active’ by this time point ($_{9}26\%_{55}$) at 3 months, while 3/17 became active at 6 months ($_{6}18\%_{42}$).

At some point before the 3 and 6 months of followup, Snellen visual acuity worsened to 20/50 or worse in 6/26 eyes ($_{10}23\%_{44}$), and 1/21 eyes ($_{1}5\%_{26}$), respectively, while it worsened to 20/200 or worse in 1/31 eyes ($_{1}3\%_{19}$) and 1/24 eyes ($_{1}4\%_{24}$), respectively. Also, at the 3 and 6 month time points, visual acuity improved to 20/50 or better in 4/16 eyes ($_{12}25\%_{44}$) and 3/13 eyes ($_{10}23\%_{53}$) respectively, and to 20/200 or better in 5/11 eyes ($_{18}45\%_{76}$) and 6/10 eyes ($_{28}60\%_{85}$). At the same durations of follow-up, mean Snellen visual acuity decreased by negligible amounts [0.09 lines (SD ±0.41) and 0.13 lines (SD ±0.31)], respectively. In addition, at 3 and 6 months, intraocular pressure (IOP) did not increase to 24 mmHg or above in any eye, and 1/28 ($_{1}4\%_{21}$). In eyes with elevated IOP at the outset of treatment, IOP decreased to 24 mmHg or below in 2 of 2 eyes (100%), both at 3 and 6 months. By these same periods of follow-up, new cystoid macular edema (CME) developed in 4/27 eyes ($_{5}15\%_{39}$) and 0/22 eyes, respectively. Cystoid macular edema resolved in 3/4 eyes with CME at baseline both at 3 and 6 months of follow-up ($_{32}75\%_{95}$).

Table 4 describes selected therapeutic outcomes in terms of persons ‘at risk’ at 3 and 6 months of followup. Discontinuation of topical corticosteroids was achieved within 3 months in 2/12 eyes ($_{5}17\%_{45}$), and at 6 months in 1/12 eyes ($_{1}8\%_{35}$). By 3 and 6 months of therapy, oral prednisone was decreased to ≤10 mg, while maintaining an ‘inactive’ inflammatory state in 1/4 patients ($_{5}25\%_{70}$), and 2/4 patients ($_{25}50\%_{85}$), respectively. During the same durations of follow-up, one or more concomitant immunomodulatory agents were discontinued in 5/20 ($_{11}25\%_{47}$) and 4/19 ($_{9}21\%_{43}$) patients, respectively. In contrast, therapy with an additional immunomodulatory agent was added in 1/22 ($_{1}5\%_{22}$) and 5/21 ($_{11}24\%_{45}$) patients, respectively.

DISCUSSION

Adalimumab, a fully human IgG1 TNF-α antibody, is being used with increasing frequency in the treatment of ocular inflammatory disease. Our report confirms the moderately beneficial effects of adalimumab therapy for ocular inflammation demonstrated in a growing number of studies. By 6 months of therapy, approximately twice (2.6 ×) as many eyes experienced improvement as did worsening of inflammation, and while visual acuity decreased slightly (0.13 lines) during therapy among these severe cases, CME resolved in the majority. A reduction in systemic corticosteroid was seen in half of patients treated. However, a similar proportion of patients required an increase in systemic immunomodulatory therapy (24%) as required a decrease in such therapy, (21%) during the relatively short follow-up period in this cohort. This, however, may be explained by the fact that many practitioners may not taper concomitant immunomodulatory therapy until longer periods of activity-free time have elapsed (e.g., a 2-year period). In addition, most patients in this cohort were pre-treated with one or more immunomodulatory agents, and adalimumab was added to the treatment regimen to these individuals in an effort to achieve long-term quiescence in the setting of a recent flare-up of inflammation. As such, this cohort represents patients with stubborn, difficult to control disease, and the 47% of eyes that transitioned from ‘active’ to ‘inactive’ inflammation may represent excellent effectiveness in this group of patients with recalcitrant disease.

Many of the early reports of use of adalimumab for ocular inflammation were case reports or small case series consisting of fewer than 10 observations. In a pilot study of 19 patients with refractory uveitis of diverse etiologies, 63% achieved control of inflammation by the end of follow-up at 12 months.[6] In another study comparing the efficacy of adalimumab and infliximab in preventing recurrences of inflammation in patients with refractory childhood uveitis, 15 of 16 children achieved control of inflammation over a median period of 12 weeks (94%), with a prevention of flare-ups in 60% of children over 40 months of follow-up in patients receiving adalimumab.[14] The more recently completed open-label, multicenter, uncontrolled ‘Review of Safety and Effectiveness with Adalimumab in Patients with Active Ankylosing Spondylitis’ (RHAPSODY) study, which enrolled 1250 patients with active ankylosing spondylitis, included 274 patients with a history of anterior uveitis.[7] This study found that adalimumab was associated with a 51% decrease in frequency of recurrences of anterior uveitis among all enrollees (15 flares/100 person-years to 7.5 flares/100 person-years), a 68% decrease among patients who had anterior uveitis activity within 1 year prior to the start of therapy (177 flares/100 person-years to 56 flares/100 person-years), and a 50%

decrease among patients with active uveitis at the start of therapy (193 flares/100 person-years vs 96 flares/100 person years). Success by 6 months, defined as control of inflammation in our study, was achieved in a smaller proportion of eyes (47%) than in the two former reports, possibly because of a more stringent definition of success and the shorter follow-up period in the data available to date from the SITE cohort, which was conducted soon after adalimumab began to be used for ocular inflammation. However, our observed proportion with success was similar to that observed in the RHAPSODY study. In another large multicenter prospective study of 131 patients with refractory uveitis, adalimumab therapy was followed by a statistically significant decrease in anterior chamber and vitreous inflammation, more favorable logMAR visual acuity, and less systemic corticosteroid and systemic immunosuppression load, with only nine patients having severe relapses during follow-up at 6 months.[19] Additionally, a prospective trial, by Suhler and colleagues, of 31 patients with noninfectious uveitis refractory to corticosteroids and at least one immunosuppressive medication showed that adalimumab was effective in reducing inflammation in 68% of patients at 10 weeks, of whom 39% exhibited durable remission after 50 weeks.[13]

Although our conservative success criterion, requiring documentation of success at visits spanning at least 28 days, might have resulted in a lower success rate, it is arguably an appropriate definition of success. Similarly, the number of patients in whom topical corticosteroid could be discontinued was low (8%), as well as the proportion of patients in whom at least one immunomodulatory agent could be discontinued (24%). These observations also may partly reflect the short follow-up period. However, our data are consistent with a prior report suggesting a somewhat lower efficacy of adalimumab in controlling intraocular inflammation compared with infliximab in patients with uveitis.[23] In addition, as mentioned previously, the achievement of quiescence in 47% of eyes in this heavily pre-treated cohort, with particularly recalcitrant inflammation, may represent excellent effectiveness. Although all centers participating in this study were tertiary specialized centers, which tend to see more severe disease than less specialized centers, most other reports derive from tertiary centers as well.

Limitations of this retrospective, observational study include potential indications-for-treatment bias given that adalimumab generally was given to severe cases that had failed prior treatments among a population of patients managed at specialized tertiary centers. While these considerations suggest that estimates of success may be low compared with a more general population, results should be generalizable to clinicians applying the treatment in a similar setting. Because the indications for use of TNF-inhibitors have broadened since the time of this study, the average patient treated might have a less severe case, such that the average patient may fare better than in a time where this treatment tended to be reserved for the most severe cases. Additional limitations derive from the retrospective study design, and the relatively limited sample size. Regarding strengths of the study, the centers involved in the SITE Cohort Study were selected in part because of a pattern of maintaining complete records to minimize the chance of missing data.[21] Data were collected by expert ophthalmologist reviewers as per protocol in all centers to minimize ascertainment bias across all visits from the time of initiation of therapy, with uniform, protocoldriven collection of data in a system with quality control checks and protocol enforcement via site

visiting. In addition, more comprehensive analyses were carried out than have been used by most prior reports, including estimation of the risk of worsening while under adalimumab therapy, which was observed in a nontrivial minority of cases.

In summary, these data suggest that adalimumab has moderate effectiveness in controlling inflammation and is corticosteroid-sparing in a variety of ocular inflammatory conditions in this cohort of patients with recalcitrant inflammation, and is likely to result in control of inflammation about half of a group of cases, which had long-standing disease and had been treated previously with multiple other therapies. Outcomes would likely be better for less severe cases. As a fully human TNF-α inhibitor, it would seem to have value *vis-à-vis* infliximab for the management of ocular inflammatory disease in patients with non-infectious uveitis[16] by avoiding the problem of reactions mediated by anti-mouse antibodies. Few complications of uveitis or of corticosteroid treatment were observed in the cohort during the period of observation at the clinics. Data regarding long-term safety of this class of drugs have been reviewed elsewhere, and continue to be investigated. Further study with larger patient cohorts and longer duration of follow-up are required to fully characterize the efficacy of adalimumab in controlling ocular inflammation and in achieving durable remission.

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APPENDIX

Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Research Group Credit Roster

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TABLE 1

Presenting characteristics of patients with ocular inflammation at the time of starting adalimumab.

	Patients	
Characteristic	***n***	**(%)**
Patients (*n*)	32	
Age (years)		
Mean ± SD	42 ± 21	
Median (range)	48 (4–74)	
Gender: male (%)	10	31.3
Race (%)		
White	25	78.1
Black	2	6.3
Other	3	9.4
N/A	2	6.3
Diagnosis		
Anterior uveitis	15	46.9
Intermediate uveitis	3	9.4
Posterior or panuveitis	3	9.4
Scleritis	9	28.1
Other	2	6.3
Duration of inflammation (years)		
Mean ± SD	6.9 ± 8.6	
Median (range)	3.0 (0–36)	
Prior therapy (%)		
Topical corticosteroids	23	71.9
Oral corticosteroids	14	43.8
Corticosteroids via any route	27	84.4
IMT (%)		
1 IMT	9	28.1
2 IMT	13	40.6
≥3 IMT	6	18.8
Total	28	87.5
Active inflammation at treatment initiation (%) *		
Yes	16	50
No	16	50

* Among eyes at treatment initiation, 22 (38.6%) were active, 34 (59.7%) were inactive, and 1 (1.8%) had unknown inflammatory status.

IMT, immunomodulatory therapy.

TABLE 2

Treatment characteristics of patients on adalimumab

	Patients	
Characteristic	***n***	**(%)**
Duration of treatment		
Mean (years)	2.6	
Range	27 days to 6.2 years	
Therapy during adalimumab treatment		
Topical corticosteroids	20	62.5
Oral corticosteroids	7	21.9
Corticosteroids (any route)	23	71.9
IMT		
1 IMT	15	46.9
2 IMT	5	15.6
≥3 IMT	2	6.3
Discontinued adalimumab	13	40.6
Reason discontinued		
Ineffectiveness	4	30.8
Other	8	61.5
Unknown	1	7.7

IMT, immunomodulatory therapy. ‘Other’ reasons for discontinuation were one each of: skin reaction, rash, fatigue and body ache, angina, swelling of rectus muscles, retinal detachment, insurance carrier non-approval, and death from unknown cause.

TABLE 3

Therapeutic outcomes of adalimumab therapy expressed per eye ‘at risk’.

Outcome (eyes)	Characteristic required to be ‘at risk’	3 months	6 months	Overall			
		Events/ At risk	Percent with event (95% CI)	Events/ At risk	Percent with event (95% CI)	Events/eye-year	Incidence rate (95% CI)
Control of Inflammation							
Improvement of AC cells by 2 grades	≥1+ cells	4/6	0.67 (0.22–0.93)	4/5	0.80 (0.29–0.98)	8/4.36	1.84 (0.77–4.35)
Improvement of vitreous cells by 2 grades	≥1+ cells	1/1	1.00 (NA)	0/0	0 (NA)	1/0.30	3.29 (NA)
Transition from ‘active’ to ‘inactive’ inflammation	Active	7/15	0.47 (0.20–0.76)	7/15	0.47 (0.20–0.76)	16/7.55	2.12 (1.29–3.49)
Transition from ‘inactive’ to ‘active’ inflammation	Inactive	6/23	0.26 (0.09–0.55)	3/17	0.18 (0.06–0.42)	10/22.0	0.46 (0.20–1.05)
Change in VA							
Worsening of VA to ≤20/50	VA ≥20/50	6/26	0.23 (0.10–0.44)	1/21	0.05 (0.01–0.26)	10/28.5	0.35 (0.15–0.80)
Worsening of VA to ≤20/200	VA ≥20/200	1/31	0.03 (0.01–0.19)	1/24	0.04 (0.01–0.24)	1/32.9	0.03 (0.004–0.23)
Doubling of visual angle	Measurable VA	8/36	0.22 (0.11–0.39)	7/27	0.26 (0.10–0.53)	10/29.7	0.34 (0.14–0.83)
Improvement of VA from ≤20/50 to >20/50	VA ≤20/50	4/16	0.25 (0.12–0.44)	3/13	0.23 (0.09–0.46)	7/11.4	0.62 (0.34–1.13)
Improvement of VA from ≤20/200 to >20/200	VA ≤20/200	5/11	0.45 (0.18–0.76)	6/10	0.60 (0.28–0.85)	8/7.21	1.11 (0.52–2.37)
Halving of visual angle	Measurable VA	5/36	0.14 (0.05–0.32)	0/27	0 (NA)	9/35.0	0.26 (0.11–0.58)
Change in VA from baseline (lines) (mean ± SD)	Measurable VA	–0.09 ± 0.41		–0.13 ± 0.31	–		
Change in IOP							
Increase to ≥24 mmHg	IOP<24	0/34	0.00 (NA)	1/28	0.04 (0.01–0.21)	2/28.9	0.07 (0.02–0.28)
Increase to ≥30 mmHg	IOP<30	0/36	0.00 (NA)	0/30	0.00 (NA)	0/32.8	0 (NA)
Decrease to ≤24 mmHg	IOP≥24	2/2	1.00 (NA)	2/2	1.00 (NA)	2/0.04	45.6 (NA)
Decreased to ≤30 mmHg	IOP≥30	0/0	NA	0/0	NA	NA	NA (NA)
Glaucoma surgery	All eyes	0/44	0.00 (NA)	0/44	0.00 (NA)	1/40.9	0.005 (0.001–0.04)
CME							
Occurrence of CME	No CME at baseline	4/27	0.15 (0.05–0.39)	0/22	0 (NA)	6/27.9	0.22 (0.07–0.63)
Resolution of CME	CME at baseline	3/4	0.75 (0.32–0.95	3/4	0.75 (0.32–0.95)	4/1.61	2.48 (1.57–3.91)
Cataract surgery	Phakic at baseline	2/36	0.06 (0.02–0.23)	2/36	0.06 (0.02–0.23)	5/31.3	0.03 (0.01–0.12)

Varying denominators are a result of varying numbers of eyes 'at risk'. As the unit of analysis is per-eye, the correlation between paired eyes of the same patient was considered in the calculations of confidence intervals of prevalence and incidence by using generalized estimating equations (GEE).

AC, anterior chamber; NA, not applicable; VA, visual acuity; SD, standard deviation; CME, cystoid macular edema; IMT, immunomodulatory therapy. NA, confidence interval not available (no events).

TABLE 4

Therapeutic outcomes of adalimumab therapy expressed per person ‘at risk’.

		3 months	6 months	Overall			
Outcome (persons)	**Characteristic required to be ‘at risk’**	**Events/ At risk**	**Percent with event, 95% CI**	**Events/ At risk**	**Percent with event, 95% CI**	**Events/ person-year**	**Incidence rate (95% CI)**
Concomitant therapy							
Discontinuation of topical steroid	On topical steroid at baseline	2/12	0.17 (0.05–0.45)	1/12	0.08 (0.01–0.35)	6/15.4	0.39 (0.18–0.85)
Reduction of prednisone to ≤10 mg/day	>10 mg at baseline	1/4	0.25 (0.05–0.70)	2/4	0.50 (0.25–0.85)	3/1.48	2.04 (0.42–5.96)
Discontinuation of other IMT	On IMT at baseline	5/20	0.25 (0.11–0.47)	4/19	0.21 (0.09–0.43)	8/19.3	0.41 (0.19–0.89)
Addition of other IMT	All patients	1/22	0.05 (0.01–0.22)	5/21	0.24 (0.11–0.45)	5/27.7	0.18 (0.07–0.47)
Discontinuation							
Discontinuation of adalimumab	All patients	4/22	0.18 (0.07–0.39)	8/21	0.38 (0.21–0.59)	12/24.4	0.49 (0.27–0.88)

The unit of analysis is per person.

IMT, immunomodulatory therapy.