

Therapeutic Effect of Oral CF101 in Patients with Rheumatoid Arthritis: A Randomized, Double-blind, Placebo-controlled Phase II Study

Rumen M Stoilov², Rodina N Licheva³, Mariyana K Mihaylova⁴, Tatiana Reitblat⁴, Emil A Dimitrov⁵, Krasimira M Shimbova¹⁰, Girish Bhatia⁶, Ameet Pispatti⁶, Alexandra Gurman- Balbir⁷, BR Bagaria¹¹, Boytcho Aleksandrov Oparanov¹², Sari Fishman¹, Zivit Harpaz¹, Motti Farbstein¹, Shira Cohen¹, David Bristol¹, Michael H Silverman¹ and Pnina Fishman^{1*}

¹Can-Fite BioPharma Ltd., Kiryat-Matalon, 10 Bareket St., P.O Box 7537, Petach-Tikva 49170, Israel

²Multiprofile Hospital for Active Treatment "Sv. Ivan Rilski" - EAD, Clinic of Rheumatology, Sofia, Bulgaria

³Diagnostic Consulting Center-17-EOOD, Rheumatology office, Sofia, Bulgaria

⁴Barzilai Medical Center, Ashkelon, Israel

⁵Pentagon Hospital Medical Hospital & research center, Pune, India

⁶Bhatia Hospital Medical Research Society, Mumbai, India

⁷Rambam Medical Center, Haifa, Israel

⁸Diagnostic Consulting Center-Akta Medika-EOOD, Rheumatology office, Sofia, Bulgaria

⁹Multiprofile Hospital for Active Treatment "Lulin" - EAD, Clinic of Rheumatology, Sofia, Bulgaria

¹⁰University Multiprofile Hospital for Active Treatment "Dr. Georgi Stranski" – Cardiology and Rheumatology Clinic, Pelven, Bulgaria

¹¹Malpani Multispecialty Hospital, Jaipur, India

¹²Military Medical Academy - Multiprofile Hospital for Active Treatment, Clinical of Cardiology and Rheumatology, Sofia, Bulgaria

Abstract

Background: CF101, an orally bioavailable A₃ adenosine receptor (A₃AR) agonist, demonstrated very good safety and anti-inflammatory effect in Phase II clinical studies in patients with rheumatoid arthritis (RA) and psoriasis. A₃AR expression level in peripheral blood mononuclear cells has been defined as a biological predictive marker, based on a significant correlation found in a former RA Phase II study between its over expression at baseline and positive patients' response to CF101 treatment.

Methods: 79 patients were enrolled to a phase II, multicenter, randomized, double-blind, Placebo controlled, parallel-group study designed to assess the efficacy and safety of CF101 1mg vs. placebo, administered orally twice daily to patients with active RA for 12 weeks. Primary efficacy endpoint was ACR20 response at week 12 and secondary efficacy included ACR 50/70. Patients were enrolled based on A₃AR mRNA expression level, utilized as an inclusion criterion. (NCT # NCT01034306)

Results: CF101 was found to be safe and well tolerated. CF101 achieved ACR20 of 48.6%, statistically significantly higher than that of the placebo group (25.0%) at week 12 (P=0.0352). CF101 showed superiority in ACR50 and ACR70 values vs. placebo. Interestingly, ACR20, ACR50 and ACR70 response rate at week 12 in a sub-population with no prior systemic therapy was impressively higher (ACR20 75%) compared to the response of the whole patient population treated with CF101.

Conclusions: CF101 reached the primary endpoint in the current study demonstrating clear evidence of efficacy and safety when given orally as monotherapy for 12 weeks in patients with active RA.

Keywords: CF101; Adenosine receptor; Randomized; Double-blind; Prognosis

Abbreviations: A₃AR: A₃ Adenosine Receptor; RA: Rheumatoid Arthritis; PBMCs: Peripheral Blood Mononuclear Cells; IRBP: Interphotoreceptor Retinoid-binding Protein; CLP: Cecal Ligation and Puncture; LPS: Lipopolysaccharide; NF-κB: Nuclear Factor Kappa-B; TNF-α: Tumor Necrosis Factor α; RANKL: Receptor Activator of NF-κB Ligand; ESR: Erythrocyte Sedimentation Rate; NSAID: Nonsteroidal Anti-inflammatory Agent; NRI: Non-responder Imputation; ITT: Intent- To-Treat; LOCF: Last Observation Carried Forward; VAS: Visual Analog Scale; HAQ: Health Assessment Questionnaire; DI: Disability Index; AE: Adverse Events; ECGs: Electrocardiograms; SAEs: Serious AEs

Introduction

The prognosis and management of Rheumatoid Arthritis (RA) has improved dramatically due to the introduction of new therapies and early treatment. The widely used anti-TNF agents are costly, exhibit a high rate of side effects and approximately 30-40% of patients fail to respond to those agents [1,2].

In principle, treatments for RA are applied by trial and error, according to drug response, and adverse event experience. Hence, the approach for developing new modes of treatment in RA should be to identify patients who are more likely to respond to specific therapies in a safe and effective manner, i.e., personalized therapy. Currently, research is focused on the development of novel biologic therapies and small molecule drugs that will meet those requirements.

The Gi protein-associated A₃ Adenosine Receptor (A₃AR) is found

***Corresponding author:** Pnina Fishman, Ph.D., Can-Fite BioPharma, 10 Bareket St., P.O.Box 7537, Petach-Tikva 49170, Israel, Tel: 972-3-3241114; Fax: 972-3-9249378; E-mail: pnina@canfite.co.il

Received January 12, 2015; **Accepted** February 10, 2015; **Published** February 13, 2015

Citation: Stoilov RM, Licheva RN, Mihaylova MK, Reitblat T, Dimitrov EA, et al. (2014) Therapeutic Effect of Oral CF101 in Patients with Rheumatoid Arthritis: A Randomized, Double-blind, Placebo-controlled Phase II Study. Immunome Res 10: 087. doi: [10.4172/17457580.1000087](https://doi.org/10.4172/17457580.1000087)

Copyright: © 2015 Stoilov RM, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

to be highly expressed in inflammatory tissues, whereas low expression of the receptor is found in normal cells [3]. Interestingly, the high A_3AR expression level is also reflected in the Peripheral Blood Mononuclear Cells (PBMCs) of patients with inflammatory autoimmune diseases, such as RA, psoriasis and Crohn's disease compared with its expression in PBMCs derived from healthy subjects [4].

Pre-clinical pharmacology studies showed that chronic treatment with the highly selective A_3AR agonist CF101 (generically known as IB-MECA) results in an anti-inflammatory response [2,5-7]. The studies included animal models of adjuvant, collagen and tropomyosin-induced arthritis, monosodium iodoacetate-induced osteoarthritis, dextran sodium sulfate induced inflammatory bowel diseases, 2,4,6-trinitrobenzene sulfonic induced colitis and spontaneous colitis in Interleukin-10 gene deficient mice, retinal antigen Interphotoreceptor Retinoid-binding Protein (IRBP) induced experimental autoimmune uveitis, Cecal Ligation and Puncture (CLP) and lipopolysaccharide (LPS)-induced sepsis, as well as in pulmonary inflammation [8].

The mechanism of action of adenosine agonism in inflammatory conditions involves the modulation of the Wnt and the nuclear factor kappa-B (NF- κ B) signal transduction pathways, leading to the inhibition of tumor necrosis factor α (TNF- α), interleukin-6 and -12, macrophage inflammatory proteins and receptor activator of NF- κ B ligand (RANKL) [9,10].

Phase II trials have demonstrated evidence of efficacy, excellent tolerability, and a favorable therapeutic index in populations with active RA and moderate to severe plaque psoriasis, treated with an oral formulation of CF101 at doses of 1 mg, 2 mg, or 4 mg twice daily [11,12]. CF101 was safe and well-tolerated in more than 1200 patients in several Phase I and II clinical studies [10-14].

In a former Phase IIa RA clinical study, a statistically significant correlation between A_3AR expression level in patients' PBMCs at baseline and response to CF101 was noted [14]. These data raise the hypothesis that A_3AR may serve as a biological marker to predict patients' response to CF101. Thus, the current Phase II study was aimed at assessing the efficacy and safety of CF101, administered orally twice daily as a monotherapy for 12 weeks to RA patients with elevated baseline expression levels of A_3AR in their PBMCs.

Patients and Methods

Patients

Patients were required to be at the age of 18-75 years, meet the criteria of the American College of Rheumatology for RA (15), with active disease as indicated by the presence of: ≥ 6 swollen joints, ≥ 6 tender joints; and either Westergren erythrocyte sedimentation rate (ESR) of ≥ 28 mm/hour or CRP 2.0 mg/dl. An elevated expression level of PBMC A_3AR , defined as 1.5-fold over a predetermined normal population standard, following the appropriate DMARD/biologic washout period, but within 2 weeks of beginning dosing was required. Patients taking a nonsteroidal anti-inflammatory agent (NSAID), or oral corticosteroid, at a dose of ≤ 10 mg/day prednisone or equivalent that had been stable for at least 1 month prior to the A_3AR qualification visit, were allowed to enter the study providing that the dose remained stable throughout the study. All patient have signed an inform consent.

Study protocol

This was a Phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group study aimed to evaluate the efficacy and safety of 1 mg of CF101, administered orally twice daily for 12

weeks to patients with active RA and elevated baseline expression levels of PBMCs A_3AR (NCT # NCT01034306) approved by Helsinki Committee. The clinical trial was conducted at 12 investigative sites in Israel, Bulgaria and India in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and regulations, and all patients provided written informed consent prior to initiation of any study-related procedures. Washout of DMARDs, including biological agents, occurred prior to dosing and upon washout the patients had to be qualified again for inclusion in the study, including A_3AR expression level.

Efficacy

Primary efficacy endpoint was ACR20 response at week 12, with all-cause dropouts considered as non-responders (non-responder imputation [NRI]), in the Intent-To-Treat (ITT) population. Secondary efficacy endpoints included ACR20/50/70 by visit, ITT, using NRI; ACR20/50/70 by visit, ITT and evaluable population, last observation carried forward (LOCF) analysis; Disease Activity Score (DAS28) by visit; change from baseline and percent change from baseline at each visit in tender joint count (28 joint count), swollen joint count (28 joint count), patient assessment of pain by visual analog scale (VAS), patient global assessment of disease activity by VAS, physician global assessment of disease activity by VAS, Health Assessment Questionnaire (HAQ) Disability Index (DI), CRP, and Westergren ESR.

A_3AR expression level analysis

For quantification of A_3AR levels, blood samples were withdrawn to BD Vacutainer® CPT™ tube with Sodium Citrate. Cells were separated according to the manufacturer's protocol. Total RNA was extracted using RNeasy mini kit (QIAGEN) with QIAshredder Spin Columns (QIAGEN). RNA (500 ng) was reverse transcribed by high capacity cDNA reverse transcription kit (AB Applied Biosystems) according to manufacturer's protocol. Real Time PCR was performed using rotor gene 3000 RT PCR detection system (Corbette Research, Australia) according to manufactures' instruction. Briefly, The PCR primer used were 5'- GGCCAATGTTACCTACATCAC -3' [forward] and 5'- CAGGGCTAGAGAGACAATGAA -3' [reversed] for ADORA3. Processes were set as follows: Initial denaturation at 95°C for 10 min, 30 cycles of amplification including a denaturation step at 95°C for 15 sec, an annealing step at 50°C, an extension step at 72°C for 15 sec. Direct detection of PCR products monitored by measuring the fluorescence produced by the result of TaqMan probe hydrolysis after every cycle.

Safety

Adverse events (AE), vital signs and weight were assessed at baseline and at weeks 2, 4, 8, and 12; clinical laboratory safety tests were assessed at baseline and at weeks 4, 8 and 12; and 12-lead resting electrocardiograms (ECGs) were assessed at baseline and at week 12.

Statistical considerations

The sample size is based on comparison of CF101 and placebo with respect to ACR20 response rates. Assuming a response rate of 27% for placebo and a response rate of 57% for CF101, a level $\alpha=0.05$ test using the normal approximation to the binomial distribution, a sample size of 40 patients per group provided a power of approximately 80%.

All patients randomized who received at least one dose of study medication were included in efficacy and safety analyses. Efficacy analyses were calculated using the ITT and Evaluable populations. For the primary efficacy analyses of ACR20, ACR50, and ACR70 response rates for all visits, patients who discontinue prior to reaching the 12

week endpoint were considered non-responders for subsequent visits, i.e. NRI was used. For secondary efficacy analyses, missing data were imputed by a last-observation-carried-forward (LOCF) rule. Secondary analyses of the primary efficacy parameter included comparisons of CF101 to placebo at each visit. For these secondary analyses, imputation using both LOCF and NRI was used.

Results

Patient demographics, baseline disease characteristics, and disposition

Seventy nine patients were randomized to receive CF101 1 mg (n=42), or placebo (n=37). Seventy one patients (89.9%) completed 12 weeks of treatment (37 patients in the 1 mg, 34 in the placebo group). Overall 5 patients (11.9%) from the CF101 group and 3 patients (8.1%) from the placebo group discontinued study treatment due to AEs (n=1), lost to follow-up (n=1), noncompliance (n=1), or withdrawal of consent (n=4) (Figure 1).

A total of 5 patients in each treatment group were excluded from the ITT population, leaving 37 (88.1%) in the CF101 group, and 32 (86.5%) in the placebo group. Most of the patients that were excluded from the

study (4 in each treatment group) were disqualified after screening due to violation of Inclusion Criteria of elevated PBMC A₃AR expression level.

The majority of patients in the study were women (81.2%): the CF101 group had a lower proportion of women (75.7%) than the Placebo group (87.5%). All the patients in the study were White/Caucasian. Duration of disease, presented as years since diagnosis, was similar for both treatment groups. Most of the prior treatments were similar in the CF101 and placebo group, except form oral corticosteroids and additional Non Biological DMARDs which were more prevalent in the CF101 treated population. Demographic and disease data are presented in Table 1.

A₃AR expression levels

All patients were tested for the expression of A₃AR mRNA levels. 70% of all tested patients were found eligible to the study with high levels of A₃AR (≥ 1.5 units) (Figure 2).

ACR responses

Primary efficacy was assessed using ACR20 response at week 12, with all-cause dropouts considered as non-responders, in the ITT

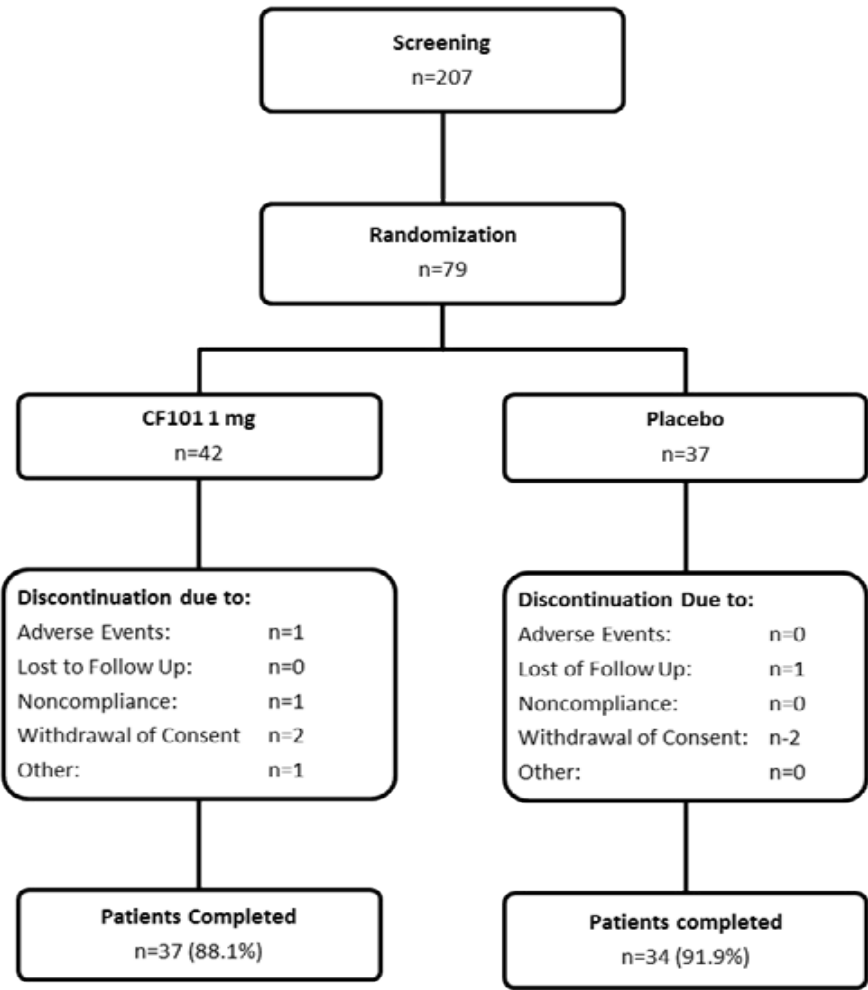
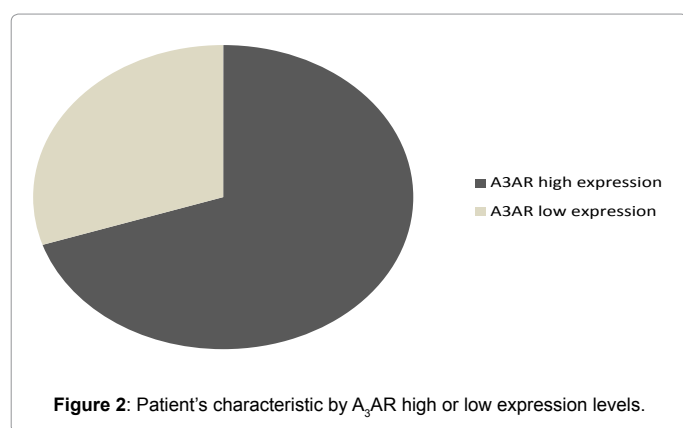


Figure 1: Patients' eligibility, randomization, assignment and discontinuation.

		CF101,1 mg	Placebo	Total
N		37	32	69
Age mean (min-max)		56.7 (24-71)	61.5 (40-74)	58.9 (24-74)
Sex N (%)	male	9 (24.3%)	13 (18.8%)	13(18.8%)
	female	28 (75.7%)	56 (81.2%)	56 (81.2%)
Race (White/Caucasian) n (%)		37 (100%)	32 (100%)	69 (100%)
Years Since diagnosis mean (min-max)		4.4 (2-36)	3.8 (2-11)	4.1 (2-36)
Prior treatment n (%)		8 (21.6%)	12 (25.0%)	16 (23.2%)
Naïve Patients		29 (78.4%)	24 (75.0%)	53 (76.8%)
Treated Patients	Intra-articular corticosteroids	1 (2.7 %)	0 (0.0%)	1 (1.4%)
	Parental corticosteroids	2 (5.4%)	1 (3.1%)	3 (4.3%)
	Oral corticosteroids	7 (18.9%)	3 (9.4%)	10 (14.5%)
	NSAIDs	11 (29.7%)	9 (28.1%)	20 (29.0%)
	Biological agents	1 (2.7%)	0 (0.0%)	1 (1.4%)
	Non Biological DMARDs	26 (70.3%)	19 (59.4%)	45 (65.2%)

Table 1: Demographic and baseline characteristics by group and overall.



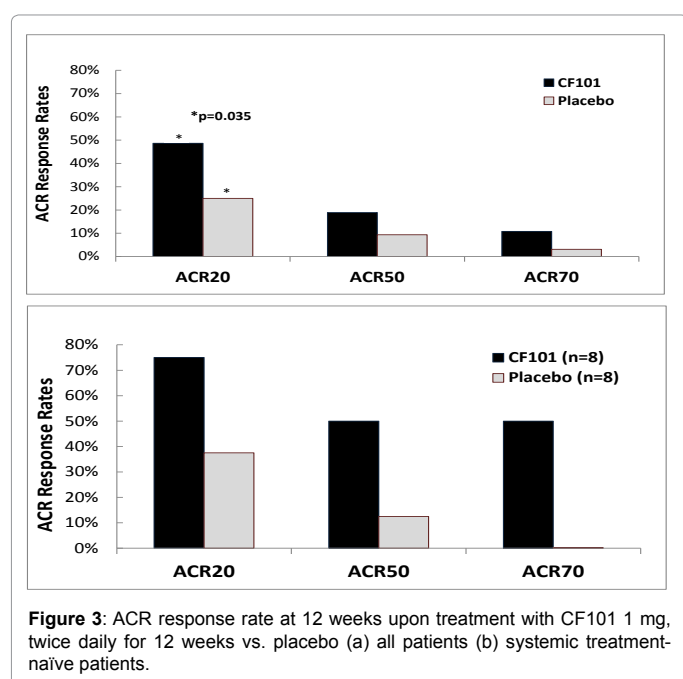
population. Responder rate was statistically significant higher in the CF101 group (48.6%) as compared with the placebo group (25.0%) at week 12 ($P=0.035$). Superiority in ACR50 and ACR70 values was observed in the CF101 treated group vs. placebo although not statistically significant. Figure 3a depicts ACR20, ACR50 and ACR70 responder rates for weeks 2, 4, 8, and 12 by treatment group.

In a subpopulation of treatment-naïve patients, with no prior systemic therapy, the response to CF101 was higher compared to the response in the whole patient population (Figure 3b). Furthermore, CF101 showed a linear improvement along the study period, data which are in line with the other Phase II studies conducted in RA and psoriasis patients (Figure 4).

Safety

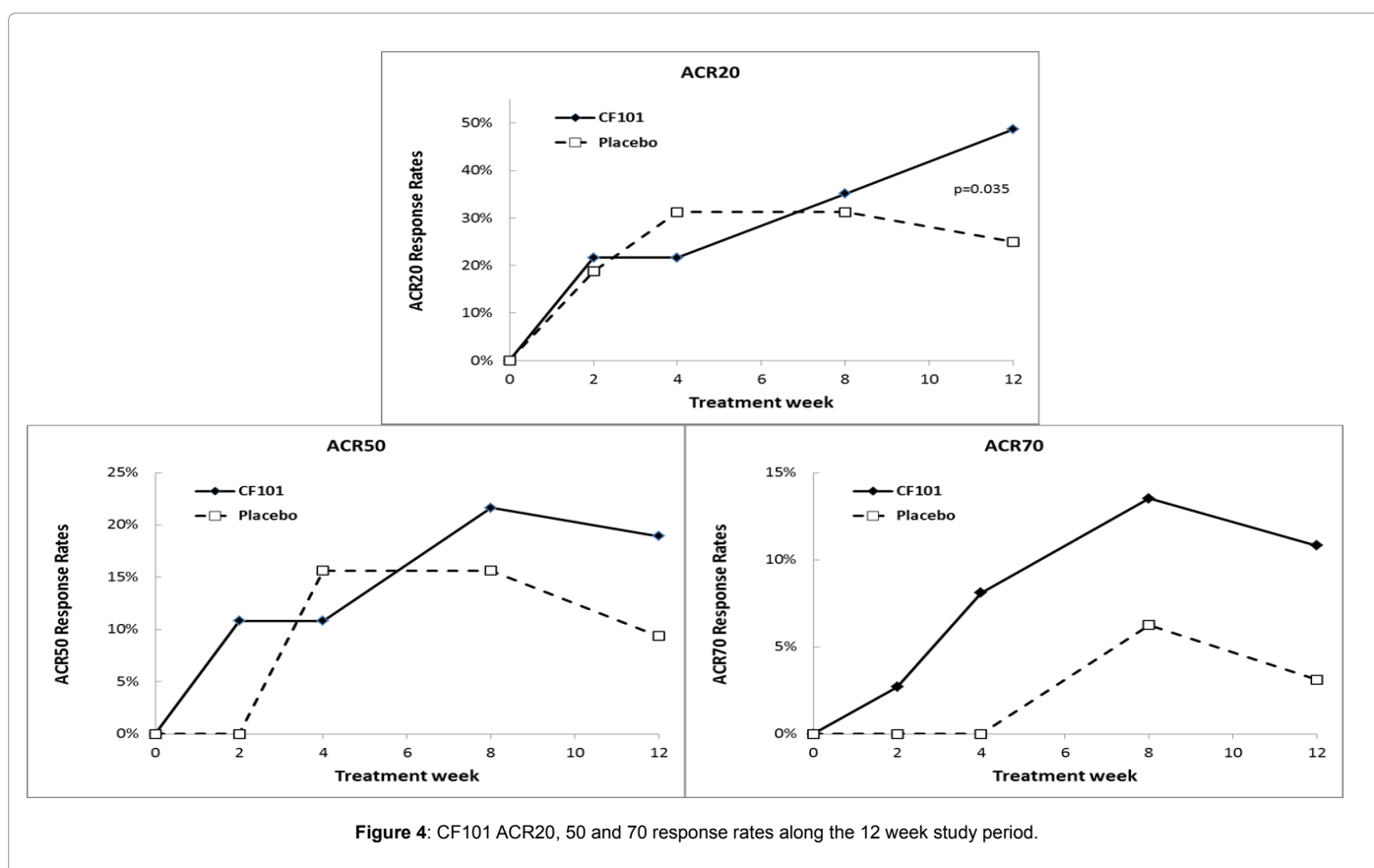
Compliance was excellent in both treatment groups. Mean compliance rate was 98.4% overall (99.4% in the CF101 group and 97.1% in the placebo group). The proportion of patients experiencing any AE was similar for both groups (16.7% for the CF101 group and 16.2% for the Placebo group). There are no apparent differences between the groups in the occurrence of specific organ system AEs and no events which suggest clinically important intolerance of CF101. Table 2 presents the number and proportion of patients who exhibited AEs according to specific organ system. None of the AEs were considered to be definitely related to study treatment. Two AEs, worsening in RA and rash, were considered possibly related to CF101. The majority of AEs were considered to be mild. One patient in the CF101 group was discontinued from the study due to a rash. This single episode of a rash was mild, required treatment with medication, was considered to be possibly related to the study drug, and resolved in 3 days.

No deaths occurred during the course of the study. Two serious AEs (SAEs) occurred during the study, one in each treatment group. Both SAEs resolved with treatment and neither was considered to be related to study treatment. One patient in the CF101 group was hospitalized for treatment of pyoderma, considered to be an SAE but unrelated to study drug. The patient was discharged a week later, at which time the event was considered to be resolved. One patient in the placebo group was hospitalized for atrial fibrillation with uncontrolled ventricular response, considered to be unrelated to study drug. The patient was treated with



System Organ Class	Adverse Events	CF101, 1 mg (N=42)	Placebo (N=37)
		n (%)	n (%)
Blood and lymphatic system disorder	Anaemia	0 (0.0)	1 (2.7)
Cardiac disorders	Atrial fibrillation	0 (0.0)	1 (2.7)
	Dry mouth	0 (0.0)	1 (2.7)
Gastrointestinal disorders	Hyperchlorhydria	0 (0.0)	1 (2.7)
	vomiting	1 (2.4)	
General disorders and administration site conditions	Burning sensation	0 (0.0)	1 (2.7)
Immune system disorders	Rheumatoid nodule	1 (2.4)	0 (0.0)
	Pyodema	1 (2.4)	0 (0.0)
Infections and infestations	Upper respiratory tract infection	1 (2.4)	0 (0.0)
	Urinary tract infection	0 (0.0)	1 (2.7)
	Albumin urine present	0 (0.0)	1 (2.7)
Investigations	Blood Creatinine increase	0 (0.0)	1 (2.7)
	Blood uric acid increase	0 (0.0)	1 (2.7)
Metabolism and nutrition disorders	Oedema peripheral	0 (0.0)	1 (2.7)
	Musculo skeletal disorder	0 (0.0)	1 (2.7)
Musculoskeletal and connective tissue disorders	Musculo skeletal pain	0 (0.0)	1 (2.7)
	Rheumatoid arthritis	1 (2.4)	0 (0.0)
Nervous system disorders	Vascular headache	1 (2.4)	0 (0.0)
	Vertigo	1 (2.4)	0 (0.0)
Skin and subcutaneous tissue disorders	Rash	1 (2.4)	0 (0.0)

Table 2: Summary of number of patients experiencing adverse events.



medication and discharged a day later with improved cardiac rhythm.

No clinically relevant changes from baseline, or differences between treatment groups, were observed regarding vital signs, weight, electrocardiogram, or safety laboratory values.

Thus, the data demonstrate that CF101 was safe and well-tolerated when administered daily as monotherapy for 12 weeks to patients with active RA. Few AEs occurred, and the proportion of patients experiencing AEs was similar for the treatment groups. No deaths, and only 2 SAEs occurred (1 in each treatment group), neither of which

were considered to be related to study treatment [15].

Discussion

In this study, we present the safety and efficacy of CF101, an A₃AR agonist, in a Phase II study in patients with rheumatoid arthritis. The A₃AR has been defined as a potent anti-inflammatory target known to induce its effect via inhibition of the Wnt and the NF-κB signal transduction pathways, resulting in apoptosis of inflammatory cells [16]. CF101 is an oral bioavailable drug which has been proved to be safe and well-tolerated in more than 1200 patients participated in RA and Psoriasis Phase II clinical studies [11-14,17]. A₃AR is over-expressed in inflammatory cells and the high expression is reflected also in the PBMCs [3]. In a former Phase IIa clinical study, a direct correlation has been found between A₃AR expression prior to treatment and patients' response to CF101 [13]. Based on these data, the inclusion criteria in this study was high level of A₃AR at baseline in comparison to that of healthy subjects. Remarkably, we have found that 70% of the patients had an over-expression of the A₃AR at baseline and therefore were eligible to be included in the study. We did not find a direct correlation between the degree of response and the expression level and assume that receptor level >1.5 unit is suffice to generate a response. The finding that 70% of the patients have receptor over-expression means that this high percent of whole population will be eligible to be treated with the drug. This personalized medicine-based tool may be useful for predicting patients' response to the drug and, to the best of our knowledge, this is the first time that RA patients were selected for a specific treatment based on a biological predictive marker, suggesting the A₃AR target concept as a personalized medicine type of approach.

CF101 treatment resulted in 48.6% response rate in ACR20 at week 12 (P=0.0352 vs. placebo). CF101 also showed superiority on ACR50 and ACR70 over placebo which was not statistically significant, most probably due to the low number of patients included in the trial. The effect of CF101 was linear and cumulative along the study period, corroborating with the effect found in our earlier RA and Psoriasis Phase II studies, showing that it takes time for the drug to induce the anti-inflammatory effect. Based on these data, we expect that longer treatment will result in a higher response rate.

Interestingly, when looking at the treatment-naïve population, CF101 demonstrate 75% ACR20 response rate vs. 37.5% in the placebo group. Even more pronounced effect has been shown in the ACR50 and ACR70 where CF101 showed 50% response rate in both vs. 10% and 0% in the placebo group, respectively. It has been documented earlier that the target A₃AR is over-expressed in early diagnosed RA patients previously untreated with DMARDS vs. healthy subjects [16]. This may explain the better response in the treatment-naïve patient population and may suggest CF101 as a first line therapy due to the excellent safety and efficacy.

The data support former studies defining A₃AR as a therapeutic and a biological predictive marker, positioning this receptor as a validated anti-inflammatory target.

Conclusion

CF101 administered orally twice daily for up to 12 weeks was safe and well tolerated inducing a statistically significant effect on disease manifestations. A₃AR can be utilized also as a biological marker to predict patients' response to CF101. The latter is suggested as a new oral and safe drug candidate to treat patients with RA.

References

- Verweij CL (2011) Pharmacogenetics: Anti-TNF therapy in RA-towards personalized medicine? *Nat Rev Rheumatol* 7: 136-138.
- Lee HT, Kim M, Joo JD, Gallos G, Chen JF, et al. (2006) A3 adenosine receptor activation decreases mortality and renal and hepatic injury in murine septic peritonitis. *Am J Physiol Regul Integr Comp Physiol* 291: 959-969.
- Ochaion A, Bar-Yehuda S, Cohn S, Del Valle L, Perez-Liz G, et al. (2006) Methotrexate enhances the anti-inflammatory effect of CF101 via up-regulation of the A3 adenosine receptor expression. *Arthritis Res Ther* 8: R169.
- Ochaion A, Bar-Yehuda S, Cohen S, Barer F, Patoka R, et al. (2009) The anti-inflammatory target A3 adenosine receptor is over-expressed in rheumatoid arthritis, psoriasis and Crohn's disease. *Cellular Immunology* 258: 115-122.
- Baharav E, Bar-Yehuda S, Madi L, Silberman D, Rath-Wolfson L, et al. (2005) The Anti-inflammatory Effect of A3 Adenosine Receptor Agonists in Murine Autoimmune Arthritis Models. *J Rheumatol* 32: 469-476.
- Bar Yehuda S, Luger D, Ochaion A, Cohen S, Patoka R, et al. (2011) Inhibition of experimental auto-immune uveitis by the A3 adenosine receptor agonist CF101. *Int J Mol Med* 28: 727-731.
- Bar-Yehuda S, Rath-Wolfson L, Del Valle L, Ochaion A, Cohen S, et al. (2009) Induction of an Antiinflammatory Effect and Prevention of Cartilage Damage in Rat Knee Osteoarthritis by CF101 Treatment. *Arthritis & rheumatism* 60: 3061-3071.
- Fishman P, Bar-Yehuda S, Liang BT, Jacobson KA (2012) Pharmacological and therapeutic effects of A3 adenosine receptor agonists. *Drug Discov Today* 17: 359-366.
- Rath-Wolfson L, Bar Yehuda S, Madi L, Ochaion A, Cohen S, et al. (2006) IB-MECA, an A3 Adenosine Receptor Agonist Prevents Bone Resorption In Rats with Adjuvant Induced Arthritis. *Clin Exp Rheum* 24: 400-406.
- van Troostenburg AR, Clark EV, Carey WDH, Warrington SJ, Kerns WD, et al. (2004) Tolerability, pharmacokinetics, and concentration-dependent hemodynamic effects of oral CF101, an A3 adenosine receptor agonist, in healthy young men. *Int J Clin Pharmacol Ther* 42: 534-542.
- David M, Akerman L, Ziv M, Kadurina M, Gospodinov D, et al. (2012) Treatment of plaque-type psoriasis with oral CF101: data from an exploratory randomized phase 2 clinical trial. *J Eur Acad Dermatol Venereol* 26: 361-367.
- Madi L, Cohn S, Ochaion A, Bar-Yehuda S, Barer F, et al. (2007) Over-expression of A3 Adenosine Receptor in PBMC of Rheumatoid Arthritis Patients: Involvement of NF-κB in mediating Receptor Level. *J Rheumatology* 34: 20-26.
- Avni I, Garzozzi HJ, Barequet IS, Segev F, Varssano D, et al. (2010) Treatment of Dry Eye Syndrome with Orally Administered CF101: Data from a Phase 2 Clinical Trial. *Ophthalmology* 117: 1287-1293.
- Silverman MH, Strand V, Markovits D, Nahir M, Reitblat T, et al. (2008) Clinical Evidence for Utilization of the A3 Adenosine Receptor as a Target to Treat Rheumatoid Arthritis: Data from a Phase II Clinical Trial. *J Rheumatology* 35: 1-7.
- Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, et al. (1988) The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 31: 315-324.
- Varani K, Massara A, Vincenzi F, Tosi A, Padovan M, et al. (2009) Normalization of A2A and A3 adenosine receptor up-regulation in rheumatoid arthritis patients by treatment with anti-tumor necrosis factor alpha but not methotrexate. *Arthritis Rheum* 60: 2880-2891.
- Antonoli L, Csóka B, Fornai M, Colucci R, Kókai E, et al. (2014) Adenosine and inflammation: what's new on the horizon? *Drug Discov Today* 19: 1051-1068.