Therapy with anti-flagellin A monoclonal antibody limits *Pseudomonas aeruginosa* invasiveness in a mouse burn wound sepsis model

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**A B S T R A C T**

Background: The aim of this study was to evaluate the effect of an anti-flagellin sub-type monoclonal antibody (anti-fla-a) on *Pseudomonas aeruginosa* infection in a mouse burn model and to assay bacterial dissemination and invasiveness.

Methods: After immediate post-burn infection with *P. aeruginosa*, mortality and morbidity (daily weight changes) were monitored in mice treated with anti-fla-a as compared to untreated mice. Bacterial dissemination and invasiveness were monitored by bacterial counts at the burn site and spleen. Three different timing regimens for anti-fla-a treatment were studied: (a) prophylaxis (pre-infection), (b) therapeutic (post-infection), and (c) combined mode.

Results: Combined regimen of anti-fla-a markedly improved survival of mice infected with *P. aeruginosa* from 6% to 96% (*p* < 0.0001), similar to treatment with Imipenem. Furthermore, a significant improvement in survival was obtained when anti-fla-a was given prior to (75% survival) or post-infection (50% survival). It reduced bacterial load in the spleen (*p* = 0.01), preventing bacterial sepsis.

Conclusion: Anti-fla-a is effective in reducing mortality and morbidity in murine *P. aeruginosa*-infected burn model.

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**1. Introduction**

Patients suffering from major burns have extensive disruption of the skin barrier, with a concurrent suppression of the immune system [1–3]. These conditions expose the burn area to bacterial wound colonization that can lead to burn wound infection, sepsis, multi-organ failure and subsequent death [1–6]. Bacterial infection is the leading cause of death in major burns (responsible to 50–80% of overall thermal injury mortality), and *Pseudomonas aeruginosa* is the most prevalent pathogen isolated from burn wound infections [5] mainly due to its high persistence in the environment and its high intrinsic and acquired antibiotic resistance [7–9]. Moreover, excessive antibiotic pressure in burn units has resulted in the
emergence of multidrug-resistant strains of \textit{P. aeruginosa} [5,10]. Therefore, supplemental approaches to antibiotic therapy such as immunotherapy, that can target centrally important virulence factors implicated in \textit{P. aeruginosa}-mediated lethality, have been extensively investigated [11,12].

Flagellin protein, the principal component of bacterial flagellum, has long been recognized as an important virulence factor in \textit{Pseudomonas} infections [13,14]. Flagellin’s effects are mediated via binding to Toll-5 receptor, TLR-5 [15], whose activation results in a profound inflammatory response [16]. Structure-function-studies revealed specific N’- and C’-terminal domains responsible for flagellin binding, pro-inflammatory signaling [15,17], and flagellar protofilament assembly and bacterial motility [18]. Since more than 95% of clinical \textit{P. aeruginosa} isolates are flagellated (with either type-a or type-b flagellin) [19], the precise mechanism(s) by which anti-flagellin antibodies protect animals in experimental models of \textit{P. aeruginosa} infection, have not yet been fully elucidated.

In a previous study, we showed that antibodies raised against the highly conserved N’-terminal region of \textit{P. aeruginosa} flagellin dramatically improved the survival of mice in two different mouse models of lethal \textit{Pseudomonas} infections [22]. Therefore, this study was aimed to further elucidate the primary mechanism of protection afforded by anti-\textit{Pseudomonas} flagellin antibodies through employment of a mouse monoclonal antibody raised against this virulence factor. Specifically, we chose to work with a previously described anti-\textit{Pseudomonas} type-a flagellin monoclonal antibody (termed anti-fla-a in this study) which was raised against \textit{P. aeruginosa}-derived flagellin [19] and evaluate its specificity and therapeutic potential against a clinical strain of \textit{P. aeruginosa} using a murine lethal infected burn wound sepsis model. Furthermore, the effects of (anti-fla-a) on the local and systemic dissemination of the bacteria were investigated.

2. Materials and methods

2.1. Anti-\textit{P. aeruginosa} flagellin type-a and -b antibodies

The mouse hybridoma FA6IIG5 (IgG3) raised against \textit{P. aeruginosa} bacterium harvesting flagellum type a [19] was obtained from ATCC. This hybridoma was grown in complete RPMI-1640 media and $5 \times 10^5$ cells injected into Pristane-primed, nude female mice for the generation of ascites fluid. Ascites fluid was thereafter pooled, diluted 10-fold with PBS and purified on protein-G chromatography. Following extensive dialysis against PBS, the purified monoclonal antibody was stored at $-20^\circ$C as aliquots at a concentration of 1–5 mg/ml. A polyclonal rabbit IgG raised against the N’-terminal domain (aminio acid nos. 1–156) of \textit{P. aeruginosa} flagellin type-b was prepared as previously described [20]. Commercial rabbit IgG (not exposed to any immunogen) was used as a non-specific IgG (NS-Ab) (Sigma, Rehovot, Israel) control in the in vivo experiments.

2.2. Preparation of \textit{P. aeruginosa} flagellin proteins

Purified, recombinant (E.coli-produced) N’-terminal \textit{P. aeruginosa} flagellin types a and b (PAK and PA01 cDNA sequences) as well as the full-length flagellin proteins of both sub-types were prepared as previously described [22]. Exotoxin-A (List Biological Laboratories Inc., USA) was also included in immunoblots as a negative control protein.

2.3. Live bacterial ELISA screen

Laboratory \textit{P. aeruginosa} strains (PA01 and PAK) as well as a panel of different \textit{P. aeruginosa} clinical strains including PA409 were grown overnight and diluted to an optical density of 0.2. One hundred ml of this culture was allowed to bind for 60 min at 37°C to ELISA plates coated with poly-l-lysine. Plates were washed with PBS/Tween-20, blocked for 60 min at room temperature with 1% BSA and incubated with anti-fla-a (111–1000 ng/ml) for 30 min at 37°C with constant shaking. Thereafter plates were taken for colorimetry assay with 5,5'-tetramethylbenzidine substrate (TMB) used for detection of peroxidase activity following incubation with a peroxidase goat anti-mouse IgG (Zymed, CA).

2.4. Immunoblots

100 ng of purified, recombinantly-produced PA flagellin proteins were electrophoresed on SDS-PAGE gels (In-Vitrogen, CA), electro blotted onto Nitrocellulose and probed with anti-fla-a (final concentration = 0.5 $\mu$g/ml). Following washing with PBS/0.4% Tween-20, blots were incubated with peroxidase conjugated goat anti-mouse IgG (H+L; Zymed, 1:10,000 dilution) and taken for enhanced chemiluminescence (ECL).

2.5. Survival studies using mice

Female CBL57 inbred mice, 18–20 g (Harlan Laboratories, Rehovot, Israel) were housed in specific pathogen free conditions using individually ventilated cages (IVC, Techniplast, Italy) in a central animal research facility. The facility maintains an environment of controlled temperature and relative humidity, with a 12-h light/dark cycle and laminar airflow compartments. The mice were supplied with sterile bedding, food and water. Each experimental group included 12 mice per group. All procedures, care and handling of the animals were reviewed and approved by the Tel-Aviv Medical Center Institutional Animal Care and Use Committee. A burn-wound sepsis model previously described by us was used to study the efficacy of antibodies [23,24]. In this model a non-lethal full-thickness burn wound consisting of 6–8% of the body surface area was induced in the right posterior flank area of mice. Infection was induced immediately after burn formation and fluid resuscitation by subeschar injection of 0.1 ml of a logarithmic culture of \textit{P. aeruginosa} clinical strain PA409, which was shown to harbor antigenic flagellin type-a. The infecting bacterial inoculum was prepared on a brain heart infusion broth (BHI, Becton-Dickinson) with agitation (180 rpm) at 37°C for 5–6 h. The cells were harvested (optical density of 0.8 at 620 nm), centrifuged and resuspended in a sterile BHI. The number of infected bacteria was verified by
plating serial dilutions of the injected inocula onto BHI agar plates. Based on previous data on the lethal dose (LD) of P. aeruginosa PA409 [23] an inoculum of $3 \times 10^6$ was used for all the in vivo studies corresponding to 5 times LD50 of the bacterium.

### 2.6. Treatment modalities

Prior to each in vivo experiment, freshly prepared antibody solutions were diluted in PBS to the desired concentration. Negative controls for anti-fla-a included a non-specific antibody (NS-Ab) and a polyclonal anti-P. aeruginosa flagellin type-b IgG fraction [22]. Imipenem freshly prepared before each experiment in PBS (0.01 M, pH 7.2) was used for the P. aeruginosa conventional systemic antibiotic control group. Anti-fla-a was given intraperitoneally as a combined regimen (0.05 mg 4 h before infection and at 4 h and once daily for 3 days after infection). Anti-fla-a was further studied in 2 other regimens: prophylaxis (pre-infection: 0.05 mg at 4 h before infection) and treatment (post-infection: 0.05 mg at 4 h and 20 h after infection). Imipenem was given intraperitoneally 0.5 mg 4 h after infection and twice daily for 4 days. Both NS-Ab and polyclonal anti-flagellin type-b were given as combined (pre- and post-infection) regimens, similarly to anti-fla-a (0.5 mg 4 h before infection and at 4 h and once daily for 3 days after infection).

### 2.7. Morbidity and mortality follow-up

Morbidity and mortality post-PA409 injection was the primary outcome used to assess the in vivo efficacy of the anti-fla-a treatment. Mortality was monitored daily in both control and experimental groups for a period of 14 days from induction of infected burns. Morbidity was determined by monitoring the individual mouse’s daily weight changes. The mice were individually tagged and weighed before the infected burn induction and afterwards were weighed on days 1, 2, 3, 7, and 14 after burn infection. Relative body weight (%) was defined as the average body weight of each group at a point of time, relatively to the average baseline (pre-infected-burn) body weight (defined as 100%). Non-surviving mice at each point of time were excluded from the average body weight calculations.

### 2.8. Bacterial proliferation, dissemination and burn histopathology

Bacterial proliferation and dissemination was studied in the anti-fla-a-treated group and in the control groups (non-infected burn group, infected non-burned group and non-treated infected burn group). Surviving mice were sacrificed ($n = 4$) from each group at each time point at various time intervals from infection (6 h, 1, and 2 days), and bacterial counts were taken from the burn areas (as a measure of local proliferation) and from the spleen (as a measure of systemic dissemination [bacteremia]). Samples from each animal’s burn area and spleen were taken aseptically, weighed, homogenized and resuspended in a sterile saline solution. Bacterial counts of P. aeruginosa per gram of tissue (eschar or spleen) were determined by serial dilutions of the sample and by colony counting on the BHI agar plates after an overnight incubation. The average concentrations of P. aeruginosa in the burn and in the spleen were calculated from an average of bacterial counts obtained from three mice that were sacrificed at each time point.

### 2.9. Statistical analysis

Statistics were run in Stata version 7 (Stata Corp., College Station, Texas). The differences between the anti-fla-a-treated groups and the non-treated or the control NS IgG-treated groups were analyzed. Dichotomous outcomes were evaluated by Fisher’s exact test, and continuous variables by Student’s t-test. All tests were two-sided and a $p < 0.05$ was considered statistically significant. Each fitting curve point represents the average value of surviving mice in that group at that point in time. Non-surviving mice were excluded from the average calculation and were regarded as “blank” rather than zero.

### 3. Results

#### 3.1. Specificity of anti-fla-a to Pseudomonas flagellin

To confirm the specificity of the anti-fla-a towards Pseudomonas strains harboring flagellin proteins, laboratory P. aeruginosa strains PAK (flagellin type-a) and PA01 (flagellin type-b) as well as a panel of clinical P. aeruginosa isolates, were screened for anti-fla-a binding in a live bacterial assay. Immobilization of P. aeruginosa bacteria to coated ELISA plates followed by addition of anti-fla-a clearly confirmed the specificity of this monoclonal antibody towards type-a flagellin since positive reactivity was only observed towards PAK and one clinical P. aeruginosa isolate, strain PA409 (Fig. 1A). Further confirmation for specificity of anti-fla-a binding towards P. aeruginosa flagellin type-a was observed from immunoblots. In these studies, anti-fla-a binding was only observed towards the full-length P. aeruginosa flagellin type a protein (Fig. 1B, lane 3), with no binding towards the full length type b flagellin (lane 4) or N-terminal flagellin types a (lane 1) and b (lane 2) domains. As anticipated, a control protein of exotoxin A (lane 5) was not recognized by anti-fla-a.

#### 3.2. Anti-fla-a is protective against P. aeruginosa infection in passive administration

To study the efficacy of anti-fla-a against P. aeruginosa infection and elucidate their local and systemic effects in vivo, we used our established infected burn wound sepsis model [23] using the clinical strain of P. aeruginosa, PA409, confirmed as a type-a flagellin serotype (Fig. 1). In this model, neither burn or infection alone were sufficient to elicit mortality. However, in the infected burn groups, mortality increased by elevating bacterial inoculum injected subeschar. Infected burn, with inoculum of $3 \times 10^6$, $6 \times 10^6$, $1 \times 10^7$ and $5 \times 10^6$ CFU per burn, resulted within 14 days in 83%, 92%, 100% and 100% mortality, respectively. Most cases of fatality occurred within the first four days. An inocula of $3 \times 10^6$ CFU per burn corresponding to 5 times lethal dose fifty (LD50) of the bacterium, was chosen for the in vivo studies. Anti-fla-a (at a...
total amount of 0.25 mg) decreased mortality of PA409-infected burn-mice from 94% (34/36), to 4% (1/24) \( p < 0.0001 \), when monoclonal antibodies were administrated in a combined regimen, prior and post-bacterial infection. Control mice that received either of the control IgG fractions exhibited essentially complete mortality (96% mortality (23/24), \( p = 0.8 \) for the NS-Ab group; 100% (12/12) for the polyclonal IgG group). The results achieved with anti-fla-a treatment were equivalent to treatment with Imipenem (4% mortality), as shown in Fig. 2A.

Daily weight changes over time post-bacterial challenge is shown in Fig. 2B. Groups treated with anti-fla-a and Imipenem revealed a rapid weight loss in the first 2 days, followed by a steady weight gain in the surviving mice reaching constant weight at 2 weeks after infection. Non-treated infected burn and NS-Ab-treated groups displayed a rapid weight loss in surviving mice until 100% mortality. Encouraged by these in vivo findings whereby anti-fla-a was given as a combined regimen, we further studied its efficacy when administered in two additional modes: prophylaxis (given only before infection) and treatment (given only after infection). Fig. 3A shows that anti-fla-a administered in all three regimens

Fig. 2 – In vivo efficacy of anti-fla-a against 
Pseudomonas aeruginosa
PA409 infection in infected burn sepsis model during passive immunization. Mice were infected with \( 3 \times 10^7 \) PA409 CFU per burn, followed by different treatment modalities. Panel A: survival in the non-treated and non-specific antibodies-treated groups (6% and 4%, respectively) was significantly lower than that of the anti-fla-a-treated group (96%). Survival in the Imipenem-treated group (96%) was equivalent to that of the anti-fla-a treated group. Anti-flagellin-b-treated control group displayed no survival. Error bars (standard deviation) were determined from an average of two or three independent experiments. Panel B: daily weight changes over time revealed a rapid weight loss, maximal on day 2, followed by a steady weight gain, reaching constant weight at 2 weeks post-infection. Groups treated with anti-fla-a and Imipenem demonstrated on day 2 post-infection less weight loss than the untreated and non-specific monoclonal antibodies-treated groups. The latter 2 groups continued to lose weight until 100% mortality.

Fig. 1 – Anti-fla-a recognition of 
Pseudomonas
strains by live ELISA and immunoblot analysis. Panel A: laboratory (PA01, PAK) and clinical 
Pseudomonas
isolates (strain #’s 201, 35225, 409, 183, 184, 185 and 188) were bound to coated ELISA plates (see Section 2) and probed with anti-fla-a. Colorimetric analysis indicated the specificity of this monoclonal antibody solely towards 
Pseudomonas
strains harboring type-a flagellin. Panel B: Anti-fla-a binding towards 
P. aeruginosa
flagellin protein by immunoblot analysis. Anti-fla-a bound only full-length flagellin type a (lane 3) but not flagellin type b (lane 4). N’-terminal 
P. aeruginosa
flagellin types a (lane 1) or b (lane 2) were essentially devoid of reactivity towards anti-fla-a, as was Exotoxin (lane 5).
reduced mortality rates compared to the untreated infected burn mice group. Mortality rates of the combined, prophylaxis (pre-infection) and treatment (post-infection) regimens were 4% ($p < 0.0001$), 25% ($p < 0.0001$), and 50% ($p = 0.001$), respectively, compared to 94% mortality in the non-treated infected burn groups. Morbidity in the different anti-fla-a regimens, as expressed by daily weight changes, paralleled survival results. Maximal weight loss occurred on day 2 post-infection, with a subsequently gradual weight gain (Fig. 3B).

Fig. 4 – Bacterial counts in mice infected with PA409 in the infected burn-wound sepsis model and the effect of anti-fla-a on bacterial dissemination. Bacterial counts assessed ($n = 3$ from each group at each time point) in the burn area and in the spleen during two days after subeschar infection of PA409 ($3 \times 10^5$ CFU per mouse). Bacterial proliferation was maximal 24 h after infection induction both in the infected burn group and the anti-fla-a-treated group. Anti-fla-a-treated group had significantly lower bacterial counts in the spleen compared to the non-treated infected burn group ($p = 0.001$).

4. Discussion

This study demonstrates the profound in vivo efficacy of an anti-flagellin type-a at doses of 0.05–0.25 mg against a clinical $P. aeruginosa$ isolate in a lethal burn wound infection model in mice. This monoclonal antibody provided significant protection in mice challenged with up to five times lethal doses of a clinical isolate of $P. aeruginosa$ with equivalent levels of protection observed with Imipenem, the conventional antibiotic used to treat $Pseudomonas$ infections in the hospital setting. The protective effect observed with anti-fla-a was a specific effect since pre-immune or a polyclonal IgG fraction raised against N-terminal type-b flagellin were both totally devoid in preventing $P. aeruginosa$-induced mortality.

To assess the in vivo efficacy of anti-fla-a we chose a murine burn wound sepsis model previously adapted by us in which mortality is driven via the dual presence of a burn injury with $P. aeruginosa$ infection, in which mortality was found to be directly proportional to the infecting inoculum [23,24]. Murine...
body weight loss observed in this model was attributed to the sepsis state after burn wound infection, with a vicious cycle of decreased appetite (lower food and water intake) and dehydration. No parenteral fluid was administered after burn wound infection.

Passive immunization with anti-fla-a given in a combined regimen (before and after infection induction) resulted in a dramatic reduction in mortality rates, in marked contrast with the control IgG antibody groups (Fig. 2A). The data described herein confirms the seminal study by Rosok et al. [19], whereby F65IGS monoclonal antibodies afforded prophyactic protection at doses of 10–50 μg when given as a treatment paradigm. The potency and efficacy of the anti-fla-a mAb initially reported by Rosok [19] and confirmed in this present study, presumably highlights the optimal methodological approach adapted by Rosok [19] in generating the mAb. In that study, immunization was performed with P. aeruginosa-derived flagellin type a protein. Thereafter, the critical hybridoma screen utilized intact P. aeruginosa bacterium on ELISA as opposed to employment of a coated, purified antigen. Using this optimal screening approach, (as adapted by us in Fig. 1A to discriminate between type a and b flagellin), anti-fla-a mAb was identified as a lead mAb.

Administration with anti-fla-a reduced morbidity as well (Fig. 2B). Mice body weight loss in the anti-fla-a-treated groups was significantly lower than in the control groups (Fig. 2B). Body weight changes within the 2-week follow-up paralleled the survival results and were similar to the Imipenem-treated group, as seen in Fig. 2B.

Non-specific immunoglobulins have been used previously against P. aeruginosa infection, given both locally and systematically, with various treatment effectiveness results [25,26]. In this current study, treatment with a pre-immune IgG still resulted in similar mortality and morbidity rates as the non-treated groups, with no apparent anti-bacterial effect. In contrast, anti-fla-a significantly lowered mortality and morbidity rates, whereas treatment with a high-titer polyclonal anti-flagellin type-b IgG, previously shown to be highly neutralizing against PA01 bacteria [22], failed to affect mortality rates using PA409. These data indicate that the absolute neutralizing specificity of the anti-fla-a is solely toward P. aeruginosa bacteria harboring the type-a flagellin protein.

As a caveat to our previous studies which demonstrated a remarkable in vivo efficacy of a polyclonal anti-N-terminal flagellin type-b IgG towards its homologous P. aeruginosa bacteria [22], it is highly plausible that a similar epitope-targeted type-a flagellin IgG might neutralize lethality associated with strain PA409. This is likely to be due to prevention of binding of a critical hexapeptide stretch (amino acids 88–97), which is critical for binding to the Toll-5 receptor. Interestingly, the anti-fla-a epitope however, appears to be directed downstream from amino acid 156 according to the immunoblot analysis (Fig. 1B), indicating the presence of a second, proinflammatory motif within the C'-terminal of P. aeruginosa flagellin in agreement with previously published findings [15,17]. Consequently, these findings lay credence that neutralizing antibodies could be developed by targeting both the N- and C-terminal domains and thereby providing a highly effective, bifurcating passive immunization approach to disable and neutralize P. aeruginosa bacteria.

The use of anti-flagellin antibodies for the treatment of P. aeruginosa infections has been described previously [19,20,25]. In this study, we tested the efficacy of passive immunization with anti-fla-a at three different regimens: before infection induction (prophylaxis regimen), after infection (treatment regimen), and combined regimen (before and after infection induction). All regimens displayed significantly enhanced survival compared to control antibody groups but at different potencies (Fig. 2A). The combined regimen afforded the highest survival rate (96%), followed by the prophyactic (75%) survival and treatment (50%) survival regimens. anti-fla-a given only before infection induction (prophylactic regimen) significantly lowered mortality and morbidity rates (Fig. 3A and B), suggesting a protective effect of anti-fla-a against P. aeruginosa infection. This observation is of particular importance in an era of increasing drug resistance, when strains of P. aeruginosa become prevalent in many hospitals in general, and particularly in burn units. With the use of conventional antimicrobial agents, resistant bacterial strains are likely to develop both to systemic and topical agents [5,9,10]. Nonetheless, inhibition of P. aeruginosa by anti-fla-a allows a selective antibacterial effect, without promoting the emergence of resistant strains.

In an attempt to understand the mechanism in which anti-flagella antibodies protect mice in the burn wound sepsis model, bacterial counts sampled from the burn area up to 48 h after infection induction were carried out. Similar bacterial proliferation in the non-treated and the anti-fla-a-treated groups was observed in the burn area (Fig. 4). In marked contrast, bacterial counts assayed from the spleen showed significant lower bacterial proliferation in the anti-fla-a treated groups, compared to the non-treated groups (Fig. 4). These results support the mechanism of action of anti-fla-a, which selectively inhibits the flagellar action of the bacteria and therefore reduces its ability to systemically disseminate via the blood stream. Our results would indicate that the effect of anti-fla-a is in attenuating bacterial motility at the burn site without affecting its ability to divide thereby ultimately resulting in failure of the bacteria to disseminate systemically. This mechanism supports the important role of the flagella in the progression of a local bacterial colonization into an invasive disease [25].

The protective effect of anti-fla-a given as a prophylactic regimen (pre-infection only) can be attributed to the selective blockage of the P. aeruginosa flagella, thereby interfering in its binding to the Toll-5 receptor. This monoclonal antibody-target recognition can be executed in the marginal area of the burn or in the blood stream. Treatment with anti-fla-a before infection induction allows recruitment of antibodies in the infected area, lowering the virulence of P. aeruginosa and reducing mortality rates. Anti-fla-a given prophylactically to high-risk populations such as burn patients may have an important potential in preventing P. aeruginosa infections. Moreover, even after infection has established, these antibodies may be used as effective therapy, decreasing the morbidity and mortality rates. Indeed, such a mechanism might involve mAb-mediated neutralization of shedded, pro-inflammatory P. aeruginosa flagellin present in the systemic circulation.

In the era of increasing antibiotic resistance, a monoclonal antibody therapy approach might provide a novel therapeutic...
paradigm. In the case of P. aeruginosa infections, the data described herein further supports the notion that such an approach to target a P. aeruginosa noxious molecule, namely flagellin, might represent a promising modality for prevention and treatment of infected burns.

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