

Safety and efficacy of tigecycline in complicated and uncomplicated pelvic inflammatory disease

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Abstract. – OBJECTIVE: Tigecycline is a gly-cylcycline antimicrobial structurally related to minocycline, with a wide spectrum of activity that includes anaerobes and typical and atypical microorganisms causing pelvic inflammatory disease (PID). This study aimed to evaluate efficacy and safety of tigecycline in complicated PID and un-complicated PID after the failure of first-line antibiotic therapy.

PATIENTS AND METHODS: Between May 2014 and April 2016 at the 2nd Unit of Obstetrics and Gynecology, Santa Chiara Hospital of Pisa a pilot study on 20 women with mild/moderate PID after the failure of first-line antibiotic therapy and on 8 women with complicated PID was conducted. The treatment protocol was 10-day course of tigecycline, with a loading dose of 100 mg intravenously (i.v.) at day one and then 50 mg IV twice daily. The primary endpoint was to evaluate tigecycline's efficacy in terms of clinical response to test-of-cure (TOC) at the end of therapy and 30 days after the last dose. Clinical response during therapy and safety were analyzed as well.

RESULTS: A total of 28 women were enrolled, and 25 patients completed the study protocol, because 3 patients reported adverse drug effects resulting in treatment interruption. PID was mainly caused by *Chlamydia*, *Gardnerella*, *Mycoplasma/Ureaplasma*. Tigecycline showed a 100% remission of signs and symptoms in patients resistant to first-line antibiotic regimen and in patients with complicated PID. Moreover, tigecycline showed good tolerability and compliance.

CONCLUSIONS: Despite the limited sample size, tigecycline seemed an effective and safe treatment for women with complicated/resistant PID. Nevertheless, further clinical trials are needed to confirm these results.

Key Words:

Pelvic inflammatory disease (PID), Tubo-ovarian abscess, Tigecycline.

Introduction

Pelvic inflammatory disease (PID) is a common clinical condition consisting of ascending infection from the lower genital tract to the upper genital tract. PID affects approximately 8% of reproductive-age women in the United States¹, comprising a spectrum of inflammatory disorders of the upper female genital tract, such as endometritis, salpingitis, tubo-ovarian abscesses, and pelvic peritonitis². The etiology of acute PID is usually polymicrobial with a wide variety of microorganisms involved. Most frequent bacteria involved are *N. gonorrhoeae*, *C. trachomatis*, *Mycoplasma spp* (particularly *Mycoplasma genitalium*), anaerobic and aerobic bacteria often belonging to normal vaginal microflora (e.g., *Prevotella spp*, Gram-negative anaerobic rods, *Peptostreptococci spp*, *Gardnerella vaginalis*, *Escherichia coli*, *Haemophilus influenzae*, and aerobic streptococci)³⁻⁷. Up to 70% of cases are non-gonococcal and non-chlamydial infections and these infections are more often associated with severe PID and have worse prognosis for future fertility^{5,6}. As consequence of the polymicrobial nature, PID is treated with antibiotics with a wide spectrum of activity⁸⁻¹¹. Although clinical diagnosis of acute PID is still difficult¹²⁻¹³ due to the mild-moderate severity of acute signs and symptoms, long-term sequelae can be serious and include infertility, ectopic pregnancy, recurrent episodes of PID, and chronic pelvic pain¹⁴⁻¹⁹.

Despite that recent reviews regarding PID management, noted that most antibiotic regimens resulted in fairly similar excellent clinical and microbiologic cure rates (primarily

for cervical *N. gonorrhoea* and *C. trachomatis*), further studies are needed to define the proper regimen(s) to prevent PID sequelae^{10,20-22}. Unfortunately, the optimal treatment strategy in complicated PID is still doubtful. A variety of antibiotic regimens have been used, without reaching optimal results. Current clinical practice includes the use of multiple agents to cover most common pathogens responsible of the disease but the best combination of agents remains still unknown. Concerning PID complications, three predictors of infertility have been identified^{23,24}: (1) duration of symptoms (> 72 hours) before starting therapy; (2) recurrent PID; (3) non-gonococcal PID^{14,25-27}.

Given that, every single regimen should guarantee an optimal clinical cure rate and an optimal microbiological control, in order to prevent recurrences.

Oral therapies appear to have similar clinical efficacy in mild or moderate PID as many randomized trials have demonstrated^{28,29}. Likewise, in case of absent clinical response to oral antimicrobial therapy or tubo-ovarian abscess, parenteral therapy, and hospitalization are recommended⁸⁻⁹.

Parenteral therapies provide for same drugs used in oral regimens, so, in case of resistance, antibiotics could result ineffective even if administered intravenously, explaining the prevalence long-term sequelae related to the disease.

Tigecycline is a semisynthetic glycylycine that received approval from the US Food and Drug Administration (FDA) for complicated intra-abdominal infections and complicated skin and skin structure infections³⁰⁻³¹. Tigecycline has a potent antibacterial activity against a broad spectrum of gram-positive, gram-negative and anaerobic micro-organisms included *Bacteroides spp.*, multidrug-resistant pathogens³¹⁻³⁵ and intracellular pathogens such as *Chlamydia* and *Mycoplasma*.

Notably, tigecycline is not affected by most of the mechanisms of resistance to tetracycline encountered in bacteria³⁴, being effective in bacteria resistant to other antibiotic classes, such as β -lactams and fluoroquinolones. Considering potential tigecycline effectiveness against typical and atypical microorganisms and the approval by FDA in treating intra-abdominal complicated infections, this drug could be studied as second-line regimen for treatment of pelvic inflammatory disease.

Patients and Methods

Patients

All consecutive patients admitted to the 2nd Unit of Obstetrics and Gynaecology, Santa Chiara Hospital of Pisa between May 2014 and April 2016, with resistant or complicated PID were enrolled in the study.

Inclusion criteria were as follows: age more than 18; persistent clinical signs of PID, according to Centre for Disease Control (CDC) criteria⁸ after antibiotic treatment; patients with US diagnosis of tubo-ovarian abscess; weight less than 140 kg; normal hepatic function; negative pregnancy test.

Exclusion criteria were hypersensitivity to the drug, hepatic failure, ongoing pregnancy, urinary tract infection, abortion or surgery within the last month.

Study treatment protocol consisted of a loading dose of tigecycline 100 mg and then 50 mg twice a day for 10 days. Clinical signs and symptoms were recorded. Pre-treatment trans-vaginal (TV) ultrasound evaluation was performed in all patients.

Vaginal and cervical swabs or culture from pelvic abscess for *Chlamydia*, *Mycoplasma*, *bacteria*, and yeast were taken before therapy.

CDC⁸ recommend empiric treatment in sexually active young women and other women at risk for Sexually Transmitted Diseases (STD) experiencing pelvic or lower abdominal pain, if no cause for the illness other than PID can be identified, in the presence of cervical motion tenderness or uterine tenderness or adnexal tenderness on pelvic examination.

Presence of signs of lower genital-tract inflammation (predominance of leukocytes in vaginal secretions, cervical exudates, or cervical friability), in addition to one of the three minimum criteria of CDC clinical diagnosis, increases the specificity of the diagnosis.

Further additional criteria were used to enhance the specificity of the minimum criteria and support a diagnosis of PID, such as fever (>38°C), abnormal cervical or vaginal mucopurulent discharge, presence of abundant numbers of WBC on saline microscopy of vaginal fluid, elevated erythrocyte sedimentation rate and elevated C-reactive protein (CRP), documented infection by *N. gonorrhoeae* or *C. trachomatis*.

A Visual Analog Scale (VAS) was used to assess pain during every pelvic examination (0, no pain; 10, worst possible pain). McCor-

mack Pain Scale was used to assess rebound tenderness (0, tenderness absent; 3, rebound tenderness)³⁷.

First physical examination (day 0) included bimanual vaginal examination, evaluation of the vagina and cervix with a speculum, temperature measurement, ultrasound TV examination and laboratory assessment for CRP and WBC levels and vaginal and cervical swabs

All women enrolled in the study received treatment with tigecycline 100 mg i.v. once daily the first day and tigecycline 50 mg i.v. twice daily, for a complete cycle of therapy of 10 days. Intravenous infusions were administered approximately in 30 to 60 min.

In case of surgery, infected tissue was cultured under aerobic and anaerobic media; a sample was also used for diagnosis of chlamydial infection using DNA amplification technique.

All patients underwent a test-of-cure (TOC) visit including clinical evaluation (pelvic examination, ultrasound TV examination, and laboratory testing) at the end of the treatment and after other 30 days. Microbiology assessments were performed at TOC visits if the pre-treatment testing was positive.

In case of a tubo-ovarian abscess, an ultrasound evaluation was performed every 15 days until resolution. The primary measure of efficacy was clinical response at TOC at the end of therapy defined as a reduction over 70% in the total pain score (VAS) and tenderness score (McCormack scale), no fever, WBC count and C-reactive protein values reduction. Treatment failed if patients exhibited persisting or progressing baseline clinical signs/symptoms of infection (reduction in the tenderness score of <30% and/or elevated temperature and/or elevated WBC), development of new clinical findings suggestive of active infection or inability in completing the study protocol due to adverse events. Secondary outcomes were microbiological control rate (defined as absence of baseline organism determining PID), negative CRP results at TOC and adverse effects rate.

Results

This study involved twenty-eight patients, 20 Italians, and 8 foreigners. Median age was 33.5 (ranging between 20-48). All of the women were symptomatic, presenting with moderate or intense pelvic discomfort. One woman had

also vaginal discharge. Nine patients presented a mild/moderate increase of temperature ($\geq 38^{\circ}\text{C}$).

In seven cases laboratory tests indicated leucocytosis and elevated CRP (median WBC count and CRP level in the whole study population 11,400 mm^3/mL and respectively). Clinical examination showed in all cases adnexal and cervical motion tenderness on bimanual vaginal examination. Cervico-vaginal swabs were positive in 8 patients. *C. trachomatis* infection was found in 3 cases. No patients with *N. gonorrhoeae* infection were identified. Other relevant pathogens isolated included *E. coli*, *G. vaginalis*, *U. urealyticum* and *E. faecalis*. Patients' characteristics are presented in Table I.

Eight patients presented ultrasound images of tubo-ovarian abscess, two of them with ascites as well. Abscess major diameter ranged from 1.5 cm to 9 cm with a mean of 3.7 cm. Bilateral tubo-ovarian abscesses were diagnosed in four cases (20%). Mean maximal diameter of the bilateral abscesses in this group of women was 5.8 cm (range 3-9 cm).

Table I. Pre-treatment patients' characteristics.

Variables	Values (n = 28)
Age (median, range)	33.5 (20-48)
BMI (median, range)	22.2 (20-30)
Failure of first line antibiotic therapy, n (%)	20 (71.4)
Fever as TC > 38°C, n (%)	9 (32.1)
Pelvic pain, n (%)	28 (100)
Abnormal cervical or vaginal discharge, n (%)	1 (3.6)
WBC, mm^3/mL (median, range)	11,400 (9000-25150)
Elevated C-Reactive Protein, mg/dL (median, range)	0.95 (0.5-23.2)
Cervicovaginal swab positivity, n (%)	8 (32.1)
<i>C. trachomatis</i>	3 (10.7)
<i>N. gonorrhoeae</i>	0 (0)
<i>G. vaginalis</i>	3 (10.7)
<i>M. hominis/U. urealyticum</i>	2 (7.1)
Polymicrobial (gram+; gram-)	1 (3.6)
Negative swab, n (%)	20 (71.4)
Tubo-ovarian abscess, n (%)	8 (32.1)
Unilateral, n (%)	4 (14.3)
Bilateral, n (%)	4 (14.3)
Maximum diameter, cm (median, range)	3.7 (1.5-9)
Complicated PID, n (%)	2 (7.1)
Sepsis needing laparoscopic treatment, n (%)	2 (7.1)
Fitz-Hugh-Curtis syndrome, n (%)	2 (7.1)

In remaining patients, five cases demonstrated tubal enlargement in US exam and the others ultrasounds were negative.

Tigecycline was administered in eight patients with tubo-ovarian abscess as first-line therapy and in twenty patients in which primary antibiotic therapy failed (ceftriaxone or levofloxacin *plus* doxycycline *plus* metronidazole as US Centers for Disease Control and Prevention Guidelines recommend in outpatient treatment of PID). Primary oral antibiotic therapy failure was defined as persistence or worsening of symptoms and signs of infection after 72 h of treatment.

Only two patients underwent to laparoscopy before first-line treatment with tigecycline. They came to our observation with clinical signs of sepsis due to tubo-ovarian abscess that was drained during laparoscopy. Moreover, these patients presented Fitz-Hugh-Curtis syndrome consequent to severe chlamydial adnexal infection (positive *Chlamydia* DNA essay on abscess material). A complete cycle of tigecycline after surgery was administered.

Twenty-five patients received 10 days of tigecycline with curative effect. Adverse events reported in 10 patients were just nausea and/or vomiting, well controlled with intravenous administration of metoclopramide, although three patients stopped treatment after 3 days due to adverse gastric effects (acute gastritis; Table II).

All the patients reported a clinical benefit within 72 h of treatment and clinical evaluation at the end of the therapy and after 30 days were completely negative for signs of PID (Table III).

Cervical and vaginal swabs were repeated in 8 patients at TOC. All microbiological cultures were negative. The bacteriological success rate was 100%. Significant improvement of CRP and WBC count levels were recorded after 15 and maintained after 30 days (Figures 1 and 2).

VAS scale and McCormack Pain Scale scores improved significantly from 15 days after treatment starting (Table III, Figure 3).

Table II. Adverse effect recorded.

Variables	Values (n = 28)
Adverse effects, n (%)	
Acute gastritis (with therapy suspension)	3 (10.7)
Nausea/vomiting	10 (35.7)

Discussion

PID is one of the most frequent and important infections that occur among non-pregnant women of reproductive age, remaining a major and bothersome public health problem³⁶⁻⁴⁰. PID represents the weightiest complication of sexually transmitted diseases (STD). Unfortunately, women who acquire acute PID are at risk for long-term sequelae⁴³⁻⁴⁷. In addition, the estimated annual health care cost for PID and its complications in the United States is over \$2 billion⁴⁶, burdening on public health system negatively. PID is often a polymicrobial condition generally cured with a combination of drugs covering a huge variety of bacteria, including atypical microorganisms. No conclusive evidence that one regimen is safer or more effective than any other for the cure of PID, and there is no clear evidence for the use of nitroimidazoles (metronidazole) compared to use of other drugs with activity over anaerobes⁴⁸. An important advantage of tigecycline is that it can be used as monotherapy because of a broad spectrum of antimicrobial activity, ranging from aerobic to anaerobic bacteria, from gram-positive to gram-negative and to atypical organisms³⁰⁻³⁵. Furthermore, many pathogens involved in PID are becoming resistant to the vast majority of existing antibiotics, so a new class of antibiotic could overcome bacterial resistance with promising outcomes. Likewise, tigecycline is extensively distributed into the tissues including lung, skin, liver, heart, and bone⁴⁹ and this condition might be useful and favorable in reclaiming pelvic abscesses.

Table III. Comparison between relevant variables pre (t_0) and post-treatment after 15 days (t_{15}) and 30 days (t_{30}) in 25 patients completing treatment protocol.

Variables	Pre-treatment (t_0)	After 15 days (t_{15})	After 30 days (t_{30})	p -value (t_0 - t_{15})
CRP levels (mean \pm SD)	7.0 \pm 8.1	0.9 \pm 1.0	0.2 \pm 0.3	0.0005
WBC count (mean \pm SD)	13,152.5 \pm 4191.3	7286.7 \pm 1757.9	6807 \pm 1730.4	0.0001
VAS scale score (mean \pm SD)	8.2 \pm 1.3	1.1 \pm 1.4	0.1 \pm 0.3	0.0001
McCormack score (mean \pm SD)	2.5 \pm 0.5	0.2 \pm 0.4	–	0.0001

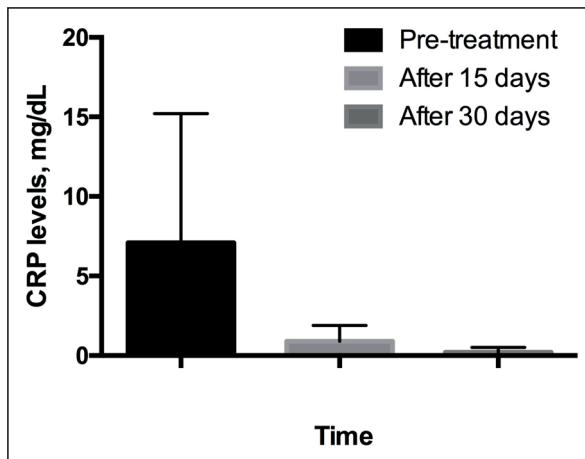


Figure 1. CRP levels comparison and changes with time in patients completing treatment (n=25).

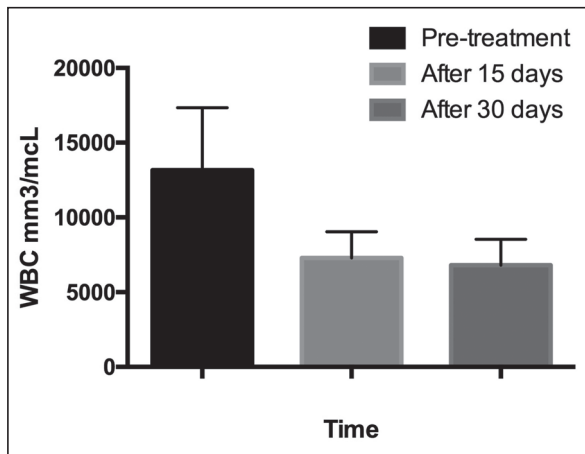


Figure 2. WBC counts levels comparison and changes with time in patients completing treatment (n=25).

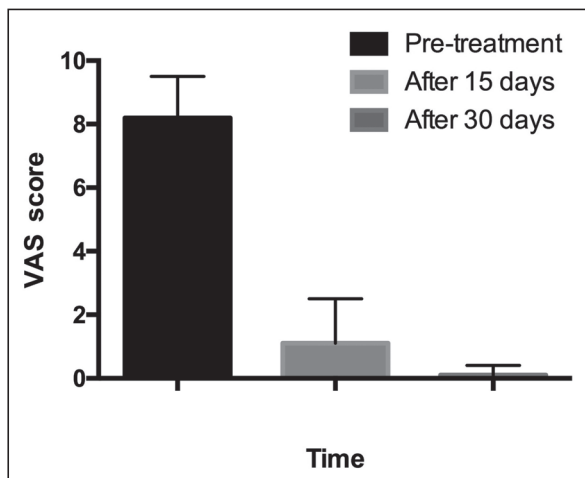


Figure 3. VAS score changes with time in patients completing treatment (n=25).

Both 2010 CDC sexually transmitted disease treatment guidelines⁸ and the 2007 European Guideline for Management of Pelvic Inflammatory Disease⁹ recommend different class of antibiotic as second-line therapy in non-responder patients, just changing delivery way (oral vs. parenteral). Considering that tigecycline belongs to a different class of antibiotics with a wider spectrum, usually, it is not affected by most of the known mechanisms of resistance to tetracycline encountered in bacteria³⁶. Tigecycline is active against resistant bacteria; thus, this drug could be beneficial in non-responder patients, where therapeutic options are still not validated and limited. This pilot study showed 89% of overall cure-rate in non-responder patients with a good tolerability and an excellent compliance. All patients reported almost the total disappearance of symptoms after 72 hours since beginning of therapy. The only adverse event reported, in agreement with previous reports, was nausea and/or vomiting nevertheless well controlled with metoclopramide^{50,51}.

Conclusions

Considering the limited sample size but with promising results, Tigecycline might be employed as second-line therapy in the mild/moderate PID and probably could be the first choice in the treatment of tubo-ovarian abscess instead of surgery. Nevertheless, randomized controlled trials to establish safety, efficacy and the length of the treatment course of this preliminary approach are needed.

Conflict of Interest

In the past two years C.T. has been paid for lectures on behalf of Pfizer, Merck Sharp and Dome, Novartis and Astellas. Other authors have no conflict of interest.

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