

Results of a Phase 1 Dose Escalation Study of Intravesical TMX-101 in Patients with Nonmuscle Invasive Bladder Cancer

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Purpose: Imiquimod, a toll like receptor 7 (TLR-7) agonist, is effective as a topical treatment for skin malignancies. TMX-101 is a liquid formulation of imiquimod. In this study we establish a safety profile of TMX-101 in patients with nonmuscle invasive bladder cancer.

Materials and Methods: We conducted a multicenter phase 1 dose escalation study in patients with nonmuscle invasive bladder cancer. Patients were included in 1 of 4 dose groups (0.05%, 0.1%, 0.2% or 0.4%) and treated with 6 weekly instillations of TMX-101, starting 2 weeks after transurethral resection of bladder tumor. Patients were evaluated weekly, and pharmacokinetic and pharmacodynamic parameters were measured.

Results: A total of 16 patients were included in the study with 4 per dose group. Two patients dropped out after instillation 2 in dose groups 1 and 2. Overall, 88 instillations were administered without serious adverse events. There were 118 adverse events, of which 84 were related to the study drug. All adverse events were mild or moderate and number or severity was not correlated with dose group. Of the related adverse events 70% were confined to the genitourinary tract and resolved without intervention. There was a dose dependent systemic uptake with low plasma levels up to dose group 3 (0.2%, 100 mg). Maximum plasma concentration in dose group 4 (0.4%, 200 mg) was 71.7 ng/ml. This is below plasma concentrations of 123 and 128 ng/ml without significant side effects measured in healthy volunteers after subcutaneous (30 mg) or oral intake (100 mg) of imiquimod, respectively.

Conclusions: Intravesical treatment with TMX-101 is safe. The side effects are common but mild and mostly limited to the genitourinary tract. There is a low systemic uptake.

Key Words: imiquimod; immunotherapy; administration, intravesical; urinary bladder neoplasms; toll-like receptor 7

BLADDER cancer causes a considerable burden for patients and seems to be the most expensive cancer.¹ Therefore, bladder cancer is an important health care problem with approximately 2.7 million patients worldwide.^{2,3} Approximately 75% of bladder cancer is

nonmuscle invasive.^{4,5} According to EAU (European Association of Urology) guidelines, the choice of treatment depends on the risk group to which the patient belongs.^{4,5} All patients should undergo TURBT followed by an immediate intravesical instillation of chemotherapy,

Abbreviations and Acronyms

AE = adverse event
BCG = bacillus Calmette-Guérin
C_{max} = maximum plasma concentration of TMX-101
CTCAE = Common Terminology Criteria for Adverse Events
DLT = dose limiting toxicity
IL = interleukin
INF = interferon
NMIBC = nonmuscle invasive bladder cancer
TLR = toll like receptor
TURBT = transurethral resection of bladder tumor

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For another article on a related topic see page 2327.

which has been shown to significantly reduce recurrence rates.⁶ This treatment is sufficient for low risk patients, but intermediate and high risk patients should receive additional treatment. The EAU and American Urological Association guidelines advise maintenance intravesical chemotherapy for intermediate risk patients, whereas patients with high risk NMIBC should receive intravesical BCG, which is considered the optimal adjuvant treatment.^{4,7,8} Despite having been the most widely used intravesical treatment for more than 35 years,⁹ BCG is associated with local and systemic side effects in a significant proportion of patients.^{10–12} Moreover, in about a third of patients, bladder cancer recurs,^{5,13} stressing the need for better and safer treatments.

Toll like receptors are proteins with a critical role in antimicrobial immunity and are key components of the innate immune system. Activation of the receptor results in an efficient antigen presentation by mature dendritic cells and enhanced production of antigen specific T cells.¹⁴ Evidence also suggests that this TLR pathway, and especially TLR-7, may be crucial in antitumor immunity.¹⁵ In the family of imidazoquinolines, the synthetic drug imiquimod (1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine) is a TLR-7 agonist and acts as an immune modulator via the MyD88 dependent pathway, with a potent antiviral and antitumor effect. Imiquimod is the active ingredient of Aldara™ cream, which is used for the treatment of genital warts, basal cell carcinoma and actinic keratosis,¹⁶ as well as carcinoma in situ of the glans penis.¹⁷ TMX-101 is an optimized formulation of imiquimod, suitable for intravesical instillation.^{18,19} Previous preclinical research showed that imiquimod has an antiproliferative effect against urothelial carcinoma in vitro,²⁰ as well as an antitumor effect²⁰ and a good safety profile in vivo.¹⁸ In this study we established a safety profile of TMX-101 in patients with low and intermediate risk NMIBC. Therefore, we conducted a phase 1 dose escalation study in which patients were treated with 6 consecutive instillations of TMX-101 after TURBT.

MATERIALS AND METHODS

After approval from the ethical committee, patients were included in this open label, multicenter, prospective phase 1 trial from June 2010 until November 2011. In this study 16 patients were treated at 4 Dutch hospitals.

Patient Selection

Patients with a bladder tumor judged to be a Ta–T1 low grade tumor were asked to participate before undergoing TURBT. Written informed consent was obtained before screening. Patients were eligible if they had pathology confirmed pTa–pT1 low grade (WHO 2004) urothelial carcinoma, if they were 18 years old or older, had an Eastern Cooperative Oncology Group performance score of 0 to 1, and if they had adequate renal, hepatic and hematological

function. Women of childbearing potential and sexually active men had to agree to use contraception during the study. Exclusion criteria were pT1 high grade bladder cancer, carcinoma in situ, high grade cytology, muscle invasive urothelial carcinoma, inability to retain an intravesical instillation for 1 hour, uncontrollable infections, history of upper urinary tract disease, immune compromised patients, active malignancies other than urothelial carcinoma and basal cell carcinoma, previous or present radiotherapy or brachytherapy, suspicion of hypersensitivity to the study drug, pregnant or breastfeeding women, participation in other studies with investigational drugs, intravesical chemotherapy within 6 months before study entry and intravesical immunotherapy within 24 months before study entry.

Treatment and Study Design

Treatment consisted of a macroscopically complete TURBT followed by 6 intravesical instillations with TMX-101 once a week for 6 weeks. The study drug TMX-101 is a 50 ml sterile liquid solution applied intravesically and retained for 1 hour. Included patients did not receive a single postoperative instillation with chemotherapy.

The study was designed as a dose escalation study with 3 to 6 patients per dose group. Dose escalation and/or patients per dose group were per protocol defined based on dose limiting toxicities and maximum tolerated dose. DLT was defined as any CTCAE grade 3 or more toxicity related to the trial medication, and/or any treatment delay of 21 days or more due to drug related adverse events. Maximum tolerated dose was defined as the highest dose level at which less than 33% of patients experienced DLT, with a minimum number of 6 patients. The schedule consisted of dose groups 1 through 4 with doubling concentrations of TMX-101 of 0.05%, 0.1%, 0.2% and 0.4%, respectively.

Patient Evaluation

The presence, severity and frequency of adverse events were assessed in the weeks after treatment, and defined according to CTCAE version 4.2. Patients were monitored routinely every week with the assessment of vital signs, blood analysis (hematology, chemistry, immunoglobulin) and urinalysis (culture, macroscopic and microscopic).

Pharmacokinetics and Pharmacodynamics

Urine samples for pharmacokinetic and pharmacodynamic investigations were obtained from all patients pre-dose and 1 hour after instillation. Furthermore, blood and urine sampling for pharmacokinetic and pharmacodynamic investigation was performed in 1 patient per dose group at points pre-dose, 0.5, 1, 1.5, 3, 4.5 and 6 hours, at treatment numbers 1 and 6. For these patients an additional written informed consent was required. Blood samples were collected in lithium-heparin tubes, transported on ice, centrifuged at 2,500 rpm for 15 minutes at 4°C within 30 minutes after collection. Aliquoted plasma was stored and shipped at -20°C upon analysis.

Plasma samples were analyzed for concentrations of the study drug and 2 of its main metabolites by liquid chromatography-mass spectroscopy with a detection range of 0.025 to 10 ng/ml. Urine samples were analyzed for TMX-101 with a detection range of 5 to 2,500 µg/ml. ELISA kits

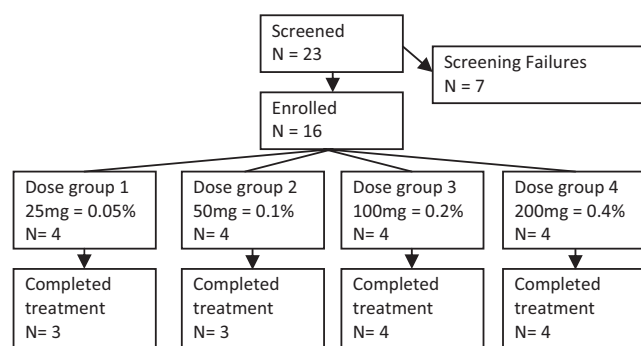


Figure 1. Patient inclusion

were used for the determination of plasma concentrations of INF- α (PBL, Interferon Source, Piscataway, New Jersey) and urinary concentrations of IL-2, IL-8, INF- γ (Pierce, Thermo Fisher Scientific Inc, Rockford, Illinois) and IL-18 (MBL, Woburn, Massachusetts), since these downstream markers may indicate a proinflammatory reaction.²¹ All plasma and urine analyses were performed by a certified external laboratory (Quotient Bioresearch Ltd., Fordham, United Kingdom).

RESULTS

At 4 Dutch sites a total of 23 patients were screened. Of these patients 7 were not enrolled because of scheduling issues (4), a histologically proven high grade tumor after TURBT (2) or an international normalized ratio greater than 1.5 times above the upper normal limit (1) (fig. 1).

Overall 16 patients were enrolled in the study with 4 in each dose group. Patient demographics are shown in table 1. In total, 88 intravesical instillations were administered. No serious adverse events occurred and no DLT was encountered in this trial.

Two patients (in dose groups 1 and 2) discontinued the treatment after instillation 2 because of AEs. The complaints resolved without intervention

Table 1. Patient characteristics

No. male (%)	11	(69)
No. female (%)	5	(31)
Age:		
Mean (SD)	58	(12.6)
Range	39–86	
No. bladder Ca history (%):		
Primary	3	(19)
Recurrent	13	(81)
Mean yrs from bladder Ca diagnosis	7.25	
No. bladder Ca stage at inclusion (%):		
T _a	15	(94)
T ₁	1	(6)
No. bladder Ca grade at inclusion (%):		
1 (1973 WHO)	5	(31)
2a (1973 WHO)	11	(69)

Table 2. Number of drug related AEs per CTCAE grade and dose group

Dose Group	Grade 1 Mild	Grade 2 Moderate	Totals
1	10	12	22
2	10	10	20
3	11	12	23
4	15	4	19
Totals	46	38	84

within 2 days. The first patient reported a burning sensation of the skin of both legs (CTCAE grade 1) unrelated to the study drug. No dermatologic and/or neurological abnormalities could be found and the burning sensations resolved without intervention. The other patient stopped because of moderate (CTCAE grade 2) burning sensations of the penis and rectum, and bladder pain related to TMX-101.

Adverse Events

All but 1 patient (in dose group 2) reported 1 or more AEs. All of the 118 reported AEs were CTCAE grade 1 or 2 and 84 AEs were related to the study drug. Of the treatment related AEs 70% was limited to the genitourinary tract. The most common reported AEs were urgency (27 AEs in 6 subjects), dysuria (12 AEs in 5 subjects), bladder spasm (8 AEs in 3 subjects), fatigue (4 AEs in 3 subjects), bladder pain (2 AEs in 2 subjects) and diarrhea (2 AEs in 2 subjects). All related AEs were mild or moderate, and generally resolved the same day without treatment. In 1 patient in the lowest dose group there was a clinically significant increased C-reactive protein (21 mg/L) which returned to normal (less than 10 mg/L) within 7 days. There was no significant difference between dose groups with regard to the number of AEs, the intensity of the AEs or the relationship with treatment (chi-square p = 0.117, table 2).

In 4 of the first 12 patients urge complaints and bladder spasms during treatment resulted in a retention time shorter than 30 minutes, possibly caused by the low pH of the instillation. Therefore, the pH of TMX-101 was increased during the study from 3.6 to 4.4 and was used for the patients in dose group 4. This modification was discussed with and approved by the ethical committee. Fewer CTCAE grade 2 events occurred in this dose group but the overall tolerability of the instillation did not improve. Mean drug retention time of the drug was 44 minutes (SD 17).

Pharmacokinetics

Blood for plasma analysis was drawn after instillations 1 and 6 of TMX-101 in 1 patient per dose group. Because the patient in the first dose group discontinued after instillation 2, another patient was included. Pharmacokinetic analysis showed

Table 3. Pharmacokinetics of TMX-101

	Dose (mg)	C _{max} (ng/ml)	Time of Max Plasma Concentration (mins)	AUC (ng*hr/ml)
Dose group 1:				
Instillation 1*	25	3.14	90	5.99
Instillation 6	25	4.33	30	9.71
Dose group 2:				
Instillation 1	50	1.64	90	5.16
Instillation 6	50	7.62	60	15.97
Dose group 3:				
Instillation 1	100	1.74	30	5.14
Instillation 6	100	2.23	30	4.54
Dose group 4:				
Instillation 1	200	59.00	90	170.10
Instillation 6	200	71.70	60	157.40

* Data for dose group 1, instillation 1, are combined from 2 patients.

low systemic uptake (less than 8 ng/ml) until dose group 3. For dose group 4 C_{max} was 71.7 ng/ml. This patient showed no systemic side effects. Maximum concentrations were reached between 30 and 90 minutes after the start of the instillation (table 3 and figure 2).

Pharmacodynamics

Plasma concentrations of INF- α were determined in 1 patient per dose group. In 2 patients plasma INF- α was detectable but no difference was found before vs after dose. Urine concentrations of IL-2, IL-8, IL-18 and INF- γ were determined in urine samples of patients before and after all instillations. Analysis of urinary IL-2 and INF- γ was limited to the first 2 dose groups due to undetectable levels. Urine levels of IL-8, IL-2 and INF- γ showed no relation to the instillations. Baseline IL-18 levels were below the detection limit in almost all patients, increased 1 hour after the instillation and returned toward baseline before the next instillation. No correlation was seen between IL-18 levels and dose group.

DISCUSSION

TMX-101 is a TLR-7 agonist suitable for intravesical use. It acts as an immune modulator in exerting a local immune response suggested to have an antitumor effect on bladder cancer.²⁰ In this phase 1 dose escalation study we demonstrated the safety of 6 consecutive intravesical treatments with TMX-101 after complete TURBT. After 6 weekly instillations with TMX-101 there were no serious AEs and no DLT was encountered. There was a limited dose dependent systemic uptake with low levels up to dose group 3.

The 16 included patients reported 84 AEs related to the study drug. The majority of these AEs were limited to the genitourinary tract such as urgency and bladder spasms. Lower urinary tract complaints are common after intravesical therapy. After treatment with the most commonly used immune modulator, BCG, up to 70% to 90% of patients reported mild complaints being predominantly irritative voiding complaints, cystitis and malaise.^{9–11} Moreover, systemic side effects (fever, nausea, vomiting, infections) also occur after BCG treatment in approximately 30% to 40% of patients.¹² The number of patients in the present trial is not sufficient for statistical comparison to AEs after BCG treatment reported in literature.

TMX-101 is a solution of imiquimod optimized for intravesical use.¹⁸ As the active ingredient of Aldara cream, imiquimod has proven its efficacy in the treatment of genital warts, basal cell carcinoma and actinic keratosis,^{16,22} and is under investigation for the treatment of other (pre)malignant lesions like vulvar intraepithelial neoplasia²³ and melanoma.^{24,25} Imiquimod is a member of the imidaziquinoline family and acts as an agonist for TLR-7. Activation of this receptor results in the maturation of dendritic cells, cytokine induction, enhanced antigen presentation and activation of the adaptive immune system. These processes account for the antiviral and antitumor effects. Furthermore, a direct proapoptotic effect on tumor cells is observed.^{26,27}

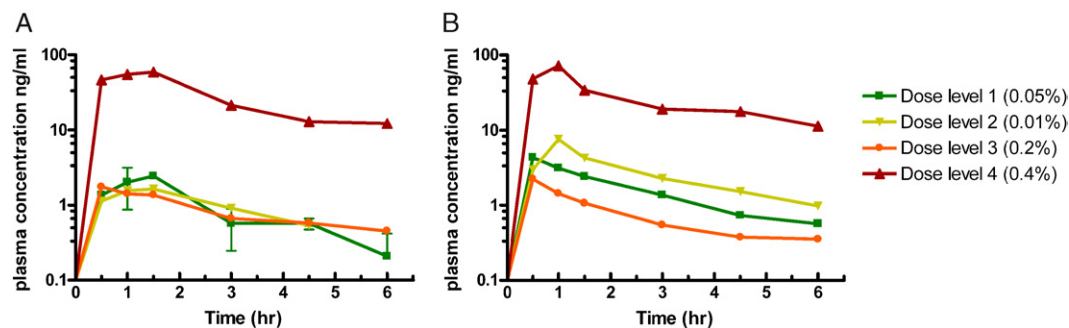


Figure 2. Pharmacokinetics. Plasma concentration of imiquimod after instillation 1 (A) and instillation 6 (B). Error bars represent standard error of mean.

It is hypothesized that analogous to the topical administration of Aldara cream for skin malignancies, bladder instillation with imiquimod might act as a local treatment for bladder cancer with limited systemic uptake. *In vitro*²⁰ and *in vivo*^{18,19} studies have shown the efficacy and safety of imiquimod as treatment for bladder cancer.

In this study we found limited systemic uptake (C_{\max} less than 8 ng/ml) after intravesical administration up to dose group 3 (0.2%). In 1 patient treated with the highest dose (200 mg, 0.4%) the systemic uptake was 71.7 ng/ml. This value is still below plasma values observed after oral intake (100 mg) or subcutaneous administration (30 mg) of imiquimod that were not associated with toxicities (123 and 128 ng/ml, respectively).^{28,29} A limitation of our study is the availability of pharmacokinetic data for only 1 patient per dose group. Because of ethical considerations and patient burden, blood sampling for pharmacokinetics until 6 hours after the instillation was only allowed in 1 patient per group.

Two patients dropped out of the study after instillation 2. Both patients reported mild to moderate complaints. One patient reported CTCAE grade 2 bladder pain, burning sensation of the penis and an irritated top of the penis, which were related to the administration of the drug. The AEs of both patients resolved without intervention. These patients were replaced to maintain 3 evaluable patients per dose group.

Compared to the aim of 1-hour retention time, the mean drug retention time in this study was 44 minutes (SD 17). Patients who voided earlier than 1 hour reported urgency and a burning sensation in the bladder. We hypothesized that the relatively low pH of the instillation (3.6) accounted for this reaction. Therefore, the 4 patients in dose group 4 received the formulation of TMX-101 with a pH of 4.4 in an attempt to optimize the tolerability. However,

it seemed that there was no difference in tolerability between the first 3 doses and the highest dose group. Another explanation for the urgency is the proinflammatory activity of imiquimod. In the initiated marker lesion part of this study, patients will receive instillations (TMX-101, 0.2% and 0.4%) with the higher pH. It will be clarified if the cause of the reduced instillation time is the pH and/or the imiquimod.

In this study we confirmed the safety of 6 consecutive intravesical instillations of the immune modulator TMX-101. We are currently conducting a marker lesion trial to evaluate the efficacy of TMX-101. Furthermore, there is ongoing preclinical work on a second generation compound, TMX-202. This is a highly specific and potent TLR-7 agonist but with a higher molecular mass and, therefore, possible less systemic uptake.³⁰ Based on the results, we consider TMX-101 a promising candidate for the intravesical treatment of patients with NMIBC, and further research will have to confirm the potential of this drug.

CONCLUSIONS

In the search for new adjuvant treatments for NMIBC, intravesical TLR-7 agonists may have a future role by acting as immune modulators. In this study we confirmed the safety of 6 intravesical instillations of TMX-101, a TLR-7 agonist. In total, 88 instillations were administered in 16 patients. There was limited dose dependent systemic uptake. The reported side effects were mild or moderate, mostly local and resolved without intervention. No dose dependent increase in frequency or severity of the adverse events was observed. A marker lesion study is ongoing to investigate the efficacy of TMX-101 as intravesical treatment for patients with NMIBC.

REFERENCES

1. Botteman MF, Pashos CL, Redaelli A et al: The health economics of bladder cancer: a comprehensive review of the published literature. *Pharmacoeconomics* 2003; **21**: 1315.
2. Ploeg M, Aben KKH and Kiemeny LA: The present and future burden of urinary bladder cancer in the world. *World J Urol* 2009; **27**: 289.
3. Siegel R, Naishadham D and Jemal A: Cancer statistics, 2012. *CA Cancer J Clin* 2012; **62**: 10.
4. Babjuk M, Oosterlinck W, Sylvester R et al: EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder, the 2011 update. *Eur Urol* 2011; **59**: 997.
5. Sylvester RJ, van der Meijden APM, Oosterlinck W et al: Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol* 2006; **49**: 466.
6. Sylvester RJ, Oosterlinck W and van der Meijden APM: A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. *J Urol* 2004; **171**: 2186.
7. Hall MC, Chang SS, Dalbagni G et al: Guideline for the management of nonmuscle invasive bladder cancer (stages Ta, T1, and Tis): 2007 update. *J Urol* 2007; **178**: 2314.
8. Gontero P, Bohle A, Malmstrom PU et al: The role of bacillus Calmette-Guerin in the treatment of non-muscle-invasive bladder cancer. *Eur Urol* 2010; **57**: 410.
9. Sylvester RJ: Bacillus Calmette-Guérin treatment of non-muscle invasive bladder cancer. *Int J Urol* 2011; **18**: 113.
10. Kresowik TP and Griffith TS: Bacillus Calmette-Guerin immunotherapy for urothelial carcinoma of the bladder. *Immunotherapy* 2009; **1**: 281.
11. Lamm DL, van der Meijden PM, Morales A et al: Incidence and treatment of complications of bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. *J Urol* 1992; **147**: 596.

12. Shang PF, Kwong J, Wang ZP et al: Intravesical Bacillus Calmette-Guerin versus epirubicin for Ta and T1 bladder cancer. *Cochrane Database Syst Rev* 2011; **5**: CD006885.
13. Fernandez-Gomez J, Madero R, Solsona E et al: Predicting nonmuscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guerin: the CUETO scoring model. *J Urol* 2009; **182**: 2195.
14. Kumar H, Kawai T and Akira S: Toll-like receptors and innate immunity. *Biochem Biophys Res Commun* 2009; **388**: 621.
15. Hemmi H, Kaisho T, Takeuchi O et al: Small anti-viral compounds activate immune cells via the TLR7 MyD88-dependent signaling pathway. *Nat Immunol* 2002; **3**: 196.
16. Geisse JK, Rich P, Pandya A et al: Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: A double-blind, randomized, vehicle-controlled study. *J Am Acad Dermatol* 2002; **47**: 390.
17. Alnajjar HM, Lam W, Bolgeri M et al: Treatment of carcinoma in situ of the glans penis with topical chemotherapy agents. *Eur Urol* 2012; **62**: 923.
18. Arentsen HC, Hulsbergen-Van de Kaa CA, Jansen CFJ et al: Pharmacokinetics and toxicity of intravesical TMX-101: a preclinical study in pigs. *BJU Int* 2011; **108**: 1210.
19. Hayashi T, Crain B, Corr M et al: Intravesical toll-like receptor 7 agonist R-837: Optimization of its formulation in an orthotopic mouse model of bladder cancer. *Int J Urol* 2010; **17**: 483.
20. Smith EB, Schwartz M, Kawamoto H et al: Antitumor effects of imidazoquinolines in urothelial cell carcinoma of the bladder. *J Urol* 2007; **177**: 2347.
21. Thalmann GN, Sermier A, Rentsch C et al: Urinary interleukin-8 and 18 predict the response of superficial bladder cancer to intravesical therapy with bacillus Calmette-Guerin. *J Urol* 2000; **164**: 2129.
22. Grussendorf-Conen EI, Jacobs S, Rubben A et al: Topical 5% imiquimod long-term treatment of cutaneous warts resistant to standard therapy modalities. *Dermatology* 2002; **205**: 139.
23. Terlou A, van Seters M, Ewing PC et al: Treatment of vulvar intraepithelial neoplasia with topical imiquimod: seven years median follow-up of a randomized clinical trial. *Gynecol Oncol* 2011; **121**: 157.
24. Narayan R, Nguyen H, Bentow JJ et al: Immunomodulation by imiquimod in patients with high risk primary melanoma. *J Invest Dermatol* 2012; **132**: 163.
25. Smyth EC, Flavin M, Pulitzer MP et al: Treatment of locally recurrent mucosal melanoma with topical imiquimod. *J Clin Oncol* 2011; **29**: E809.
26. Meyer T, Nindl I, Schmoock T et al: Induction of apoptosis by toll-like receptor-7 agonist in tissue cultures. *Br J Dermatol* 2003; **149**: 9.
27. Schon M, Bong AB, Drewniok C et al: Tumor-selective induction of apoptosis and the small-molecule immune response modifier imiquimod. *J Natl Cancer Inst* 2003; **95**: 1138.
28. Goldstein D, Hertzog P, Tomkinson E et al: Administration of imiquimod, an interferon inducer, in asymptomatic human immunodeficiency virus-infected persons to determine safety and biologic response modification. *J Infect Dis* 1998; **178**: 858.
29. Soria I, Myhre P, Horton V et al: Effect of food on the pharmacokinetics and bioavailability of oral imiquimod relative to a subcutaneous dose. *Int J Clin Pharmacol Ther* 2000; **38**: 476.
30. Falke J, Arentsen HC, Hulsbergen-Van de Kaa A et al: Pharmacokinetics and toxicity of R-837 and TMX-202 after intravesical and intravenous administration: a pre-clinical study in naive rats. *Eur Urol Suppl* 2012; **11**: E665.