CML generics:
From a hematologist perspective
story from Serbia

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Why we are talking about generics?

Serbian pharmaceutical companies are producer of good quality generics during many years (from time of former Yugoslavia), and the drug export and “know how” was a significant product of Yugoslavia and now Serbia, Slovenia, Croatia…

Those companies nowadays are also part of worldwide network of generic manufacturers like Watson-Actavis, Stada, Teva…

Generic drugs are widely used in our hospitals
They helped us to reduce costs of medical treatment and to provide more treatment to those who needed

What are the main differences between inovative/branded drug and generics?

patent and regulatory issues, approved indications
price and pricing policy for reimbursement

results from published clinical trials generally include data obtained with use of branded drugs

possible difference in manufacturing process of the chemical compound itself
difference in additional substances within the drug
difference in absorption, drug kinetic and metabolism

generally generics are approved after bioequivalent trial without long term safety and efficacy data

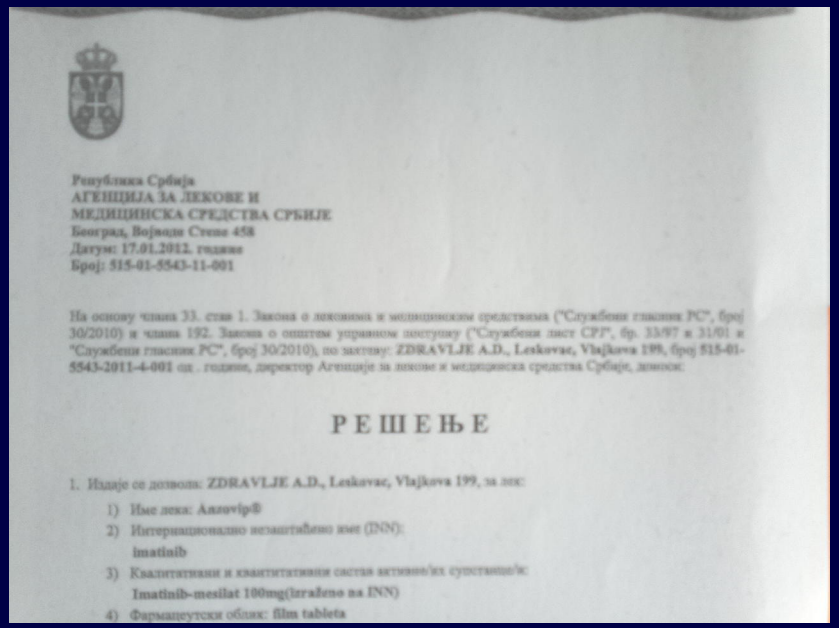
(European directives)

Issue of generic imatinib in Serbia

branded imatinib (Glivec®) was registered in Serbia in 2001, allowed for treatment on insurance in 2006

during late 2011 and first half of 2012 problems in obtaining regular monthly supply of Glivec®

Approval of generic imatinib in 2012 (Anzovip® Actavis)



Република Србија
АГЕНЦИЈА ЗА ЛЕКОВЕ И
МЕДИЦИНСКА СРЕДСТВА СРБИЈЕ
Београд, Војводе Степе 458
Датум: 17.01.2012. године
Број: 515-01-5543-11-001

На основу члана 33. став 1. Закона о лековима и медицинским средствима ("Службени гласник РС", број 30/2010) и члана 192. Закона о општем управном поступку ("Службени лист СРЈ", бр. 33/97 и 31/01 и "Службени гласник РС", број 30/2010), по захтеву: ZDRAVLJE A.D., Leskovac, Vlajkova 199, број 515-01-5543-2011-4-001 од . године, директор Агенције за лекове и медицинска средства Србије, доноси:

РЕШЕЊЕ

1. Издаје се дозвола: ZDRAVLJE A.D., Leskovac, Vlajkova 199, за лек:
   1) Име лека: Anzovip®
   2) Интернационално незаштићено име (INN):
      imatinib
   3) Квалитативни и квантитативни састав активне/их супстанце/и:
      Imatinib-mesilat 100mg(izraženo na INN)
   4) Фармацеутски облик: film tableta

Approval of generic imatinib (Anzovip)

approved by the Agency for Drugs and Medical devices of Serbia in January 2012

approved according to Drug Act as domestic drug since “Zdravlje” Leskovac is Actavis branch in Serbia

approved after bioequivalence trial in accordance with EMEA regulations for bioequivalence crossover trial (CPMP/EWP/QWP/1401/98)
based on single dose kinetics and equivalence

Questions arising ?

no practical experience with such drug in the country

different pharmaceutical form of the drug (tablets / capsules)

no enough published data about efficacy and safety of the compound

lot of conflicting data in available media (e.g. internet) concerning generic/copy drug and branded Glivec

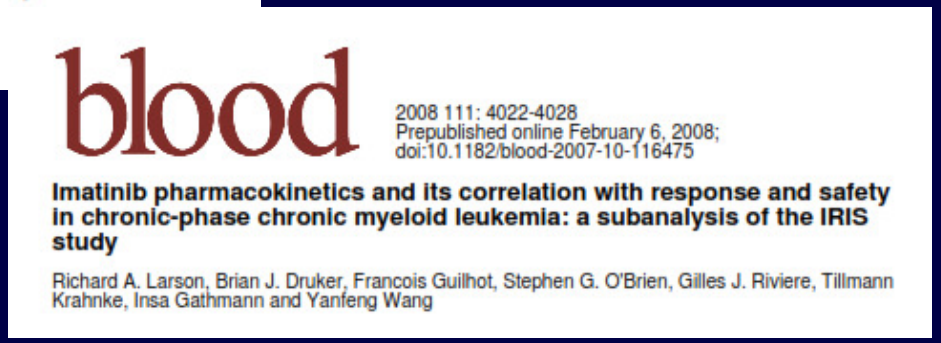
quite well known consequences of inadequate CML treatment on long run in patients (inevitable transformation of the disease...)

bad experience with unknown generic drugs during period of UN sanctions (in 90's, lot of adverse reactions, allergies...)

What we know in 2012

several forms of imatinib (alfa, beta, amorphous…)
different production technologies (alcohol or acetone crystalisation)
long term patent dispute in India (High Court in Chenai decision and patent chemists technical discussions, available on internet)

need for long term treatment and effects of trough imatinib concentration on efficacy, effects of OCT transporter protein on drug uptake and metabolism, possible side effects and tolerability of imatinib in general, long term toxicity of imatinib



What we know in 2012

published cases of inadequate response or loss of response after switch to generic imatinib

Int J Hematol
DOI 10.1007/s12185-009-0431-1

CASE REPORT

Failure of copy Imatib (CIPLA, India) to maintain hematologic and cytogenetic responses in chronic myeloid leukemia in chronic phase

Mervat Mattar

Case Reports in Oncology
Case Rep Oncol 2010;3:272–276
DOI: 10.1159/000319150
Published online: July 26, 2010
© 2010 S. Karger AG, Basel
ISSN 1662–6575
www.karger.com/cro

Hematologic Relapse after 2 Years on a Non-Authorized Copy Version of Imatinib in a Patient with Chronic Myeloid Leukemia in Chronic Phase: A Case Report

Zoubir Chouffai

JOURNAL OF MEDICAL CASE REPORTS

Case report

Open Access

Failure of a non-authorized copy product to maintain response achieved with imatinib in a patient with chronic phase chronic myeloid leukemia: a case report

Hadi Alphonse Goubran

Address: Professor of Medicine and Clinical Haematology, Faculty of Medicine, Cairo University, 73, Maadi, 1431, Cairo, Egypt

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IMPACT OF SWITCHING THERAPY FROM IMATINIB MESYLATE TO GENERIC COPY OF IMATINIB ON HEMATOLOGIC RESPONSE IN PATIENTS WITH CHRONIC PHASE CHRONIC MYELOID LEUKEMIA: SINGLE CENTER STUDY

502 | haematologica | 2011; 96(s2)

F Alwan, A Alshami, A Hatim, A Au

The National Center of Hematology, Baghdad, Iraq

loss of response in 33% of 126 pts half of them progressed

good response, 77% of patients achieved complete cytogenetic response up to 18 months (EHA 16 London)

1234

THE TREATMENT OF CHRONIC MYELOID LEUKEMIA BY IMATINIB MESYLATE GENERIC: ABOUT 26 CASES

H Eddou, S Astati, E Mahtat, H El Maaroufi, M Bouaouad, S Jennane, N Alami Drideb, K Doghmi, M Mikdame

Military Hospital Mohammed V, Rabat, Morocc

508 | haematologica | 2011; 96(s2)

Therefore, what is the standpoint of the hematologist

Agency approval is obligatory and not negotiable because it is the approval by regulatory body, by qualified team (pharmacologists)

Inadequate response could be only documented by detailed cohort analysis and follow up of patients on treatment

if the patients are not taking the drug, how to evaluate?
do we have problems concerning previous inadequate drug supply with Glivec® in certain time period?

do we have rescue for our patients?

many different questions arisen by patients, by media…

How we solved the problem

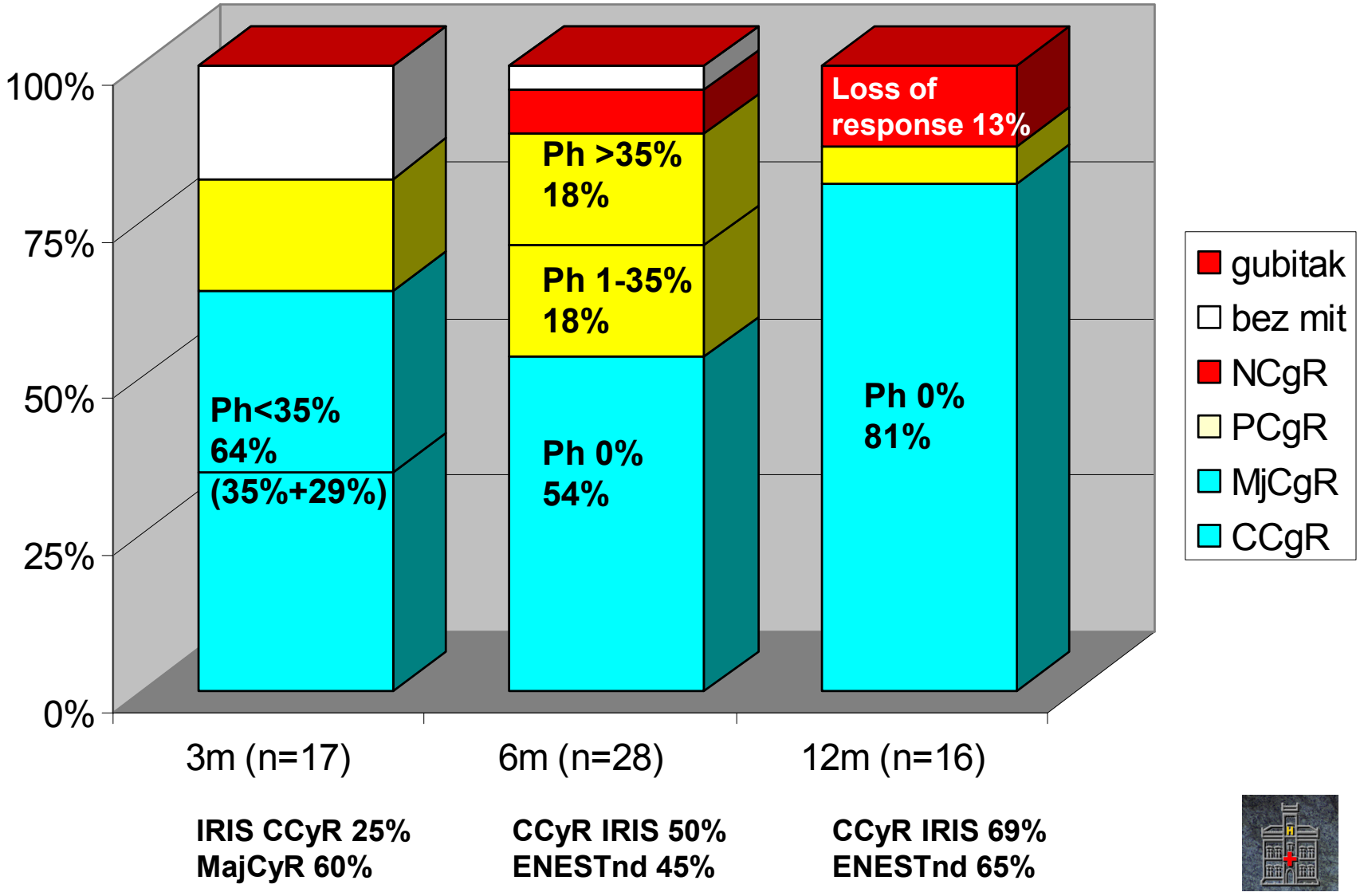
After the introduction of generic imatinib (Anzovip®) all patients were switched to generic drug (all 220 patients in Serbia, 120 pts in Clinical center Belgrade).

loss of response within 3 months of switch was noted in 7 long term treated patients (in all centers). All patients belonged to intermediate Sokal risk group, and have no loss of hematological but only loss of cytogenetic response. All were switched to nilotinib gaining full complete response again. Loss of response is also registered in small number of patients treated with branded imatinib before

careful follow up of a cohort of newly diagnosed CML patients treated with generic imatinib (Anzovip®) frontline

careful follow up of a selected patients several months after switch to generic imatinib (approximately 6 months from switch)

Effects in newly diagnosed patients

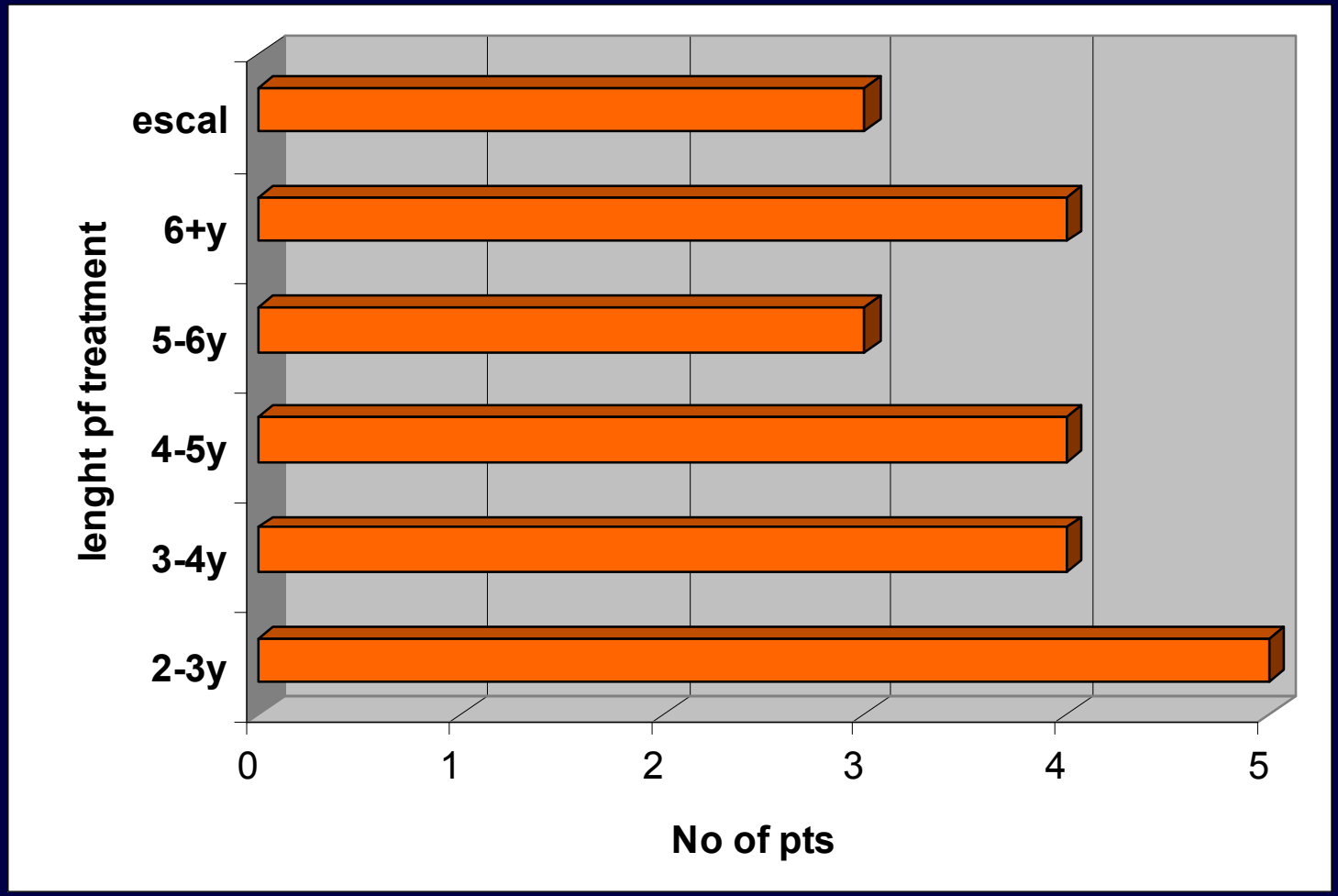


IRIS CCyR 25%
MajCyR 60%

CCyR IRIS 50%
ENESTnd 45%

CCyR IRIS 69%
ENESTnd 65%

Effects in follow up patients



none of 23 evaluated patients (included 4 on escalated dose) lost their response after switch to generic imatinib (Anzovip®) after establishment of regular drug supply

For the end

this is never ending story (we have two more generic IM registered by the Agency), but not on the market

generic imatinib, Anzovip by Zdravlje-Actavis proved to be efficient replacement of branded Glivec

long term toxicity is not different from branded compound (within 18 months of treatment)

response is similar to published data with branded imatinib and molecular response is under evaluation as well

further comparison trials should be warranted and demanded by regulatory bodies to ensure efficacy of a such treatment for severe diseases like cancer and leukemia