The use of unlicensed bone marrow-derived platelet lysate-expanded mesenchymal stromal cells in colitis : a pre-clinical study

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7LWOH SDJH

7LWOH 7KH XWLOLJDWLRQ RI XQOLFHHQVHG ER

PHVHQFK\PDO VWURPDO FHOOV LQ FRO

+DQQH 6DORPHQNDUL#KHODLQND LDLSQLOHQ#EORRGVH
)RUVJnUGFKDUG IRUVJDUG#KHOVLQNLMLDKHOVLSDFRPSDFRP
MHUH OLQGHQ#KHOVLQNL IL ODMLUSDVDDHOVQ#KHOVLQNL IL
PDWWL NRUQRQH#EORRGVHUYLEWWD NBUWWD#KROSHONL IL D
MRKDQQD Q\VWHGW#EORRGVHUYLFH IL

3KDUPDFRORJ\)DFXOW\ RI OHGLFLQH 8QLYHUVLW\ RI +HO

)LQODQG

\$GYDQFHG &HOO 7KHUHS\ &HQWUH)LQQLVK 5HG &URVV %C

)LQODQG

'HSDUWPHQW RI %DVLF 9HWHULQDU\ 6FLHQFHV)DFXOW\ RI

\$JQHV 6MJEHUJLQNDWX +HOVLQNL)LQODQG

&RUUHVSRRGL'ESDUWPHQW +HDG -RKDQQD 1\VWHGW \$GM 3URI

)LQQLVK 5HG &URVV %ORRG 6HUYLFH .LYLKDDQWLH +HOV

MRKDQQD Q\VWHGW#EORRGVHUYLFH IL

.H\ ZRUOGPHVHQFK\PDO VWURPDO FHOOV 06&V &U\RSUHVHUYDWLR

FROLWLW 5HQLQ DQJLRWHQVLQ V\VWHP

\$EVWUDFW

%DFNJURPHQFK\PDO VWURPDO FHOOV 06&V DUH D SURPLVLQJ

GLVRUGHUV EXW WKHLU HIILFDF\ LQ KXPdq LQIODPPDWRU\ ERZ

RI WKH UHVXOWV IURP YDULRXV SUHFOLQLFDO DQG FOLQLFDO ,
VWXG\ GHVLJQV

0HWKR,QVWKLW FRPSDUDWLYH SUHFOLQLFDO VWXG\ ZH FRPSDUH
VDIHW\ DQG IHDVLELOLW\ RI ERWK IUHVK DQG FU\RSUHVHUYHG
06&V ZLWKRXW DGGLWLRQDO OLFHQVLQJ LQ D GH[WUDQ VRGLXP
DQG UHJHQHUDWLYH SKDVHV RI FROLWLW %RG\ ZHLJKW PDFUR
71). FRQFHQWUDWLRQV ZHUH GHWHUPLQHG LQ ERWK SKDVHV RI
,O DQG 150 \$ OHYHOV DQG DQJLRWHQVLQ FRQYHUWLQJ HQJ\PH
FRORQ LQ WKH UHJHQHUDWLYH SKDVH RI FROLWLW

5HVXOWV WUDYHQRXVO\ DGPLQLVWHUHG 06&V H[KLELWHG PRGHV
FROLWLW E\ UHGXFHQJ ,/ SURWHLQ OHYHOV LQ WKH LQIODPH
WUHDWHG ZLWK IUHVK RU FU\RSUHVHUYHG XQOLFHQVHG 06&V D
DQG PDFURVFRSLF VFRUH UHVXOWV 3UR LQIODPPDWRU\ \$(SU
FU\RSUHVHUYHG 06&V LQ WKH FRORQ

&RQFOXVLQJ FRQFOXVLRQ ZH REVHUYHG D JRRG VDIHW\ SURILO
H[SDQG HG 06&V LQ D PRXVH SUHFOLQLFDO FROLWLW PRGHO EX
DGGLWLRQDO OLFHQVLQJ L H VXFK DV 06&V DUH DGPLQLVWHU
LQ YRROHO V\ VWHP DQG OLPLWHG WR ELRFKHPLFDO LPSURYHP
KLVWRSDWKRRJ\ RU ERG\ ZHLJKW GHYHORSPHQW

%DFNJURXQG

,QIODPPDWRU\ ERZHO GLVHDTVH ,%' DUH PXOWLIDFWRULDO LQ
LQWHVWLQDO WLVVXH EORRG\ GLDUUKHD DQG XOFHUDWLRQ 7H
GLVHDTVH 8OFHUDWLYH FROLWLW PDLQO\ PDQLIHVVV DV LQIODPP
SDWFKHV FDQ EH SUHVHQW WKURXJKRXW WKH JDVWURLQWHVW
DOWHUQDWLRQ EHWZHHQ UHPLVVLRQ DQG DQ DFWLYH GLVHDTVH
GLVHDTVH UHPLVVLRQ RU VKRUWHQ DFWLYH GLVHDTVH SHULRGV
LQIODPPDWRU\ PHGLFDWLRQ DPLQRVDOLF\ODWHV DQG FRUWL
PHWKRWUH[DWH PRQRFORQDO DQWL 71). DQWLERGLHV DQG VX
RQO\ WHPSRUDU\ UHOLHI IRU H[DPSOH GXH WR GUXJ UHVLVWD
QHHGHG DV D VXEYHW RI SDWLHQWV UHVSRRGV SRRUO\ WR WKHV
FHOOV 06&V LV RQH LQWHUHVWLQJ RSWLRQ

06&V DUH SURPLVLQJ FDQGLGDWHV IRU VXSSUHVVLQJ XQGHVLUH
DQG UHJHQHUDWLRQ> @ 06&V VHFUHHW VROXEOH IDFWRUV V
O\PSKRF\WH SUROLIHUWLRQ DQG SURPRWH LPPXQH FHOO GLIHH
VXSSUHVVLVHLQHYHQRQ LPPW FRPSOHWHO\ UHVROYHG> @ ,W KDV
QRW SURYRNH DQ RYHUW LPPXQH UHDFWLRQ IURP WKH KRWW HY
@ EXW D UHFHQW VWXG\ SUHVHQWHG FRQYLQFLQJO\ D FRPSO
EDVHG RQ DSRSWRVLV RI 06&V DQG ZKHUH DQ LPPXQH DFWLYDV
FULWLFDO IRU HIIHFWLYH LPPXQH VXSSUHVVLVRQ WKURXJK PDFU
DQWL LQIODPPDWRU\ SURSHUWLHV KDYH PDGH WKHVH FHOOV S
GLVHDTVH LQFOXGLQJ P\RFDUGLDO LQIDUFWLRQ DUWKULWLW I
VWXGLHV KDYH DOVR HYDOXDWHG WKHLU HIILFDF\ LQ WKH WUHD
DOOHYLDWHG WKH V\PSWRPV RI GH[WUDQ VRGLXP VXOIDWH '66
LQGXFHG FROLWLW EXW UHVXOWV IURP FOLQLFDO WULDOV DUH
GLIILFXOW WR WUHDW EXW JRRG RXWFRPHV PHDVXUHG DV ILV
%0 GHULYHG 06&V LQ ORFDO WUHDWPHQW RI ILVWXODV> @

06&V LQ WKH WUHDWPHQW RI SHULDQDO ILVWXODV IRXQG 06& W
RI WKHVH WULDOV RQO\ FRQFOXGHG WKH 06& WKHUDS\ WR EH D
LQIXVLRQV RI 06&V KDYL EHHQ ZHOO WROHUDWHG DQG IHDVLEO
@ RQO\ RQH RI WKH VWXGLHV KDYL GHPRQVWUDWHG HIILFDF\
)XQFWLRQDO SURSHUWLHV RI 06& PD\ EH DIIHFWHG E\ GLIIHUH
FRQGLWLRQV> @ \$OORJHQLF RU DXWRORJR XV 06&V DUH PRVW
SDVVH\WLRU UHDFK DGHTXDWH QXPEHUV RI FHOOV IRU FOLQLFD
HDVLO\ OLFHQVHG ZLWK YDULRXV F\WRNLQHV SULRU WR DGPLQLV
EXW LQ FOLQLFDO DSSOLFDWLRQV DGGLWLRQDO OLFHQVLQJ ZRX
WKH SUHFOLQLFDO VWXGLHV ZLWK DQLPDO FROLWLIV PRGHV K
PXULQH 06&V 7R RXU NQRZOHGJH DOO FOLQLFDO WULDOV KDYL
WR DGPLQLVWUDWLRQ 06& SUHSDUDWLRQV FDQ HLWKHU EH IUH
MXVW EHIRUH DGPLQLVWUDWLRQ WR SDWLHQWV RU WKH FHO
DGPLQLVWUDWLRQ \$ FU\RSUHVHUYDWLRQ VWHS LQ WKH PDQID
HQDEOHV D FRPSOHWLRQ RI DOO TXDOLW\ WHVWLQJ EHIRUH EDW
WKH DGPLQLVWUDWLRQ RI LGHQWLFDO FHOO GRVHV LQ UHSHDW
RQO\ IHDVLEOH RSWLRQ IRU 06& EDQNLQJ VWUDWHJLHV DQG LV
KRZHYHU VXJJHVV WKDW FU\RSUHVHUYHG 06&V PD\ KDYL LPSD
IUHVKO\ KDUYHVWHG 06&V IURP FRQLQXRXV FXOWXUHV> @
HIILFDF\ RI FU\RSUHVHUYHG 06&V LV FRPSDUDEOH WR IUHVK 06&
VWXGLHV WR HOXFLGDWH WKH LPSDFW RI D FU\RSUHVHUYDWLRQ
,Q WKLIV FRPSDUDWLYH SUHFOLQLFDO VWXG\ ZH LQYHVWLJDWH
H[SDQG HG KXPDQ %0 GHULYHG 06&V LQ D '66 LQGXFHG PXULQ
PLQLPDOO\ H[SDQG HG FXOWXUHG XQWLO SDVVDJH FU\RSUHV
HIIHFWLYH WR VRPH H[WHQW LQ WKH WUHDWPHQW RI DFXWH JU
SURGXFW WR LWV IUHVK XQIUR]HQ FRXQWHUSDW LQ WKH VDP
H[SDQG HG 06&V ZLWK DQ\ DGGLWLRQDO F\WRNLQHV WR EH DEO

SURGXFW L H VXFK DV 06&V DUH FXUUHQWO\ SUHSDUHG DQG DG
)LUVW ZH FRPSDUHG WKH DGPLQLVWUDWLRQ URXWHV XVLQJ
LQWUDYHQRXVO\ ,9 RU LQWUDSHULWRQHDOO\ ,3 DQG FRPSDU
WKH DFXWH SKDVH RI FROLWLW 6HFRQG ZH FRPSDUHG ,9 06& W
06& FHOOSUHSDUDWLRQV LQ WKH UHJHQHUDWLYH SKDVH RI FR
WLVVXH KHDOLQJ SURPRWLQJ HIIHFWV RI 06&V LQ WKH FRORQ E
HQJ\PH \$&(SURWHLQ H[SUHVVLHQ DQG VKHGGHQ DQG DQWL
SUHSDUDWLRQV 7KLW VWXG\ IXUWKHU GHPRQVUDWHG WKH VDI
PRGHVW WKHUDSHXWLF HIIHFW LQ WUHDWPHQW RI H[SHULPHQW
EHWZHHQ IUHVK DQG FU\RSUHVHUYHG 06&V UHPDLQHGXQHUVRQ
LQYROYPHQW LQ UHJXODWLRQ RI WKH LQWHVWLQDO UHQLQ DQ

0HWKRGV

06& H[SDQVLRQ FKDUDFWHUL]DWLRQ DQG SUHSDUDWLRQ EHIRU
+XPDQ ERQH PDUURZ ZDV KDUYHVWHG DQG 06&V ZHUH H[SDQGHC
ZHUH H[SDQGHC LQ PHGLXP FRQVLVWLQJ RI ' 0(0 ORZ JOXFRVH
VXSSOHPHQWHG ZLWK ,8 PO KHSULQ +HSDULQ /(2 ,(< P
SODWHOHW O\VDWH 3/ VXSSOHPHQW DV GHVFULEHG SUHYLRXV
—J PO VWUHSWRP\FLQ /LIH 7HFKQRORJLHV *UDQG ,VODQG 1<
ZHUH WU\SVLQLJHG ZLWK/LIHSOHQRORJLHV70 DQG UHVXVSHQGHC
1D&O KXPDQ VHUXP DOEXPLQ +6\$ \$OEXQRUP J / 2F
DGPLQLVWUDWLRQ URXWH VWXG\ RU 1D&O +6\$O\HPO
IUHVK 06&)RU FU\RSUHVHUYHG 06& SUHSDUDWLRQV WKH FH
&U\R6XUH :\$. &KHPLH 0HGLFDO *FEO 7KHFDQRSDWVHJUYHG FHOC
f& ZDWHU EDWK FHQWULIXJHG DW J IRU PLQ DIWHU D VKR
+6\$ DW FHOOV PO FU\R 06& &RPSDUDWLYH FHOOSDWFKHV

DQG WKH IUHVK 06& SUHSDUDWLRQV ZHUH SUHSDUHG IURP LQWH
XQWLO S DFFRUGLQJ WR WKH DGPLQLVWUDWLRQ VFKHGXOH

7KH 06&V ZHUH FKDUDFWHULJHG IRU FHOO VXUIDFH PDUNHUV DQ
GHVFULEHG SUHYLRXVO\> @ DQG ZHUH YHULILHG WR KDYH D W
DV GHVFULEHG E\ /DLWLQHQ HW DO > @ RVWHRJHQLF DQG DO
LPPXQRVXSSUHVLRQV\ &HOO QXPEHUV DQG YLDELO
1XFOHR&RXQWH&KH&PROHWHF \$OOHURG 'HQPDUN 7KH YLDELO
WKDZLQJ DQG ! K DIWHU WKDZLQJ GDWD QRW VKRZQ
\$QLPDOV

7KH DQLPDO H[SHULPHQWV ZHUH DSSURYHG E\ WKH QDWLR
(6\$9, DQG (6\$9, DFFRUGLQJ WR W
([SHULPHQWDWLRQ ODOH EDOE F PLFH REWDLQHG IURP 6
DJH ZHUH XVHG IRU WKH VWXG\ 7KH PLFH ZHUH KRXXVHG LQ D
KXPLGLW\ RI “ 7KH DQLPDOV ZHUH JLYHQ D 7HNODG
/DERUDWRULHV ,QGLDQDSROLV ,1 86\$ VWDDG DUEZLWKDQDQW
ZHUH ZHLJKHG GDLO\ WKURXJKRXW WKH H[SHULPHQW

6WXG\ GHVLJQ DQG LQGXFWRQ RI FROLWL

7KH VWXG\ GHVLJQ LV SUHVHQWHG LQ GHWDLO LQ)LJXUH

\$GPLQLVWUDWLRQ URXWH VWXG\ ZLWK D VKRUW IROORZ XS LQ V

7R FRPSDUH ,9 DQG ,3 06& DGPLQLVWUDWLRQ LQ WKH DFXWH S
Q LQ HDFK JURXS YLD DGPLQLVWUDWLRQ RI '66 '% 7G%
GULQNLQJ ZDWHU IRU GD\ GD\ 2Q GD\ DQG RI WKH
06&V LQ 1D&O +6\$ RU YHKLFOH 9(1D&O +6\$ Z
YHLQ RU ,3 XQGHU LVRIOXUDQH LQKDODWLRQ DQHVWKHVL D &R

KHDOWK\ FRQWURO JURXS KDG DFFHV V WR WDS ZDWHU WKURXJK
GD\ WKH PLFH ZHUH DQG DFFHFWLQJ W&RQ

)UHV K 06& YHUVXV FU\R 06& VWXG\ ZLWK RQH DGPLQLVWUDWLRQ
SKDVH RI FROLWL

7R FRPSDUH IUHV K DQG FU\RSUHVHUYHG 06&V LQ WKH UHJHQH
JURXS V Q LQ HDFK JURXS YLD DGPLQLVWUDWLRQ RI '66 LQ
UHFHLYHG WDS ZDWHU IRU GD\ GD\ 2Q GD\ DQG RI
FU\R 06&V 06&V LQ 1D&O +6\$ RU 9(1D&O
JURXS ZHUH LQMHFWHG ,9 YLD WKH WDLO YHLQ RI WKH PLFH LQ
06& XQGHU LVRIOXUDQH LQKDODWLRQ DQHVWKHVLD 7KH KHDO
WKH H[SHULPHQW DQG UHFHLYHG QR 06&V RU 9(2Q GD\ WKH
LVRIOXUDQH DQHVWKHVLD

0DFURVFRSLF DVVHVPHQW RI LQIODPPDWLRQ

8SRQ VDFULILFH PDFURVFRSLF LQIODPPDWLRQ ZDV VFRUH LQ V
OHQJWKV ZHUH PHDVXUH 7KH FRORQV ZHUH RSHQH ORQJLWX
IURP QrupDO ORRVH DQG OLTXLG 7KH FRORQV ZHUH
DIWHU ZKLFK FRORQLF HGHPD DQG SUHVHQFH RI EORRG LQ WKH
ZKHU QRQH SUHVHQW DQG FOHDUO\ REVHUYDEOH \$OO WH
PDFURVFRSLF VFRUH VFDOH

3UHSUDWLRQ RI WLVVXH VDP SOHV

7R FRPSDUH WKH KLVWRSDWKRRJLFDO FKDQJHV LQ PLFH UHFH
ZHUH IL[HG LQ QHXWUDO EXIIHUG IRUPDOLQ 6LJPD \$OGULFK
LQ SDUDIILQ EORFNV)RU ERWK VWXGLHV WLVVXH VDP SOHV F
LPPXQRFKHPLFDO DQDO\HV 3LHFHV RI SUR[LPD FRORQ ZHUH
PPRO O 1D&O PPRO O 1D&O 2&O PPRO O JOXFRVFRSLF PPRO O

PPRO O 01R62 PLQ DIWHU ZKLFK WKH VDP SOHV ZHUH FHQWU
VXSHUQDWDQW ZDV FROOHFWHG IRU FRUWLF RVWHURQH DQG \$&(
0LFURVFRSLF DVVHV VPHQW RI LQIODPPDWLRQ

&RORQ VOLGHV ZHUH VWDLQHG ZLWK KHPDWR[\OLQ DQG HRVLQ
,QIODPPDWLRQ DFWLYLW\ PXFRVDO DWURSK\ DQG FU\SW UHJHO
D JUDGH RI WR E\ D WUDLQHG SDWKRORJLVW ,QIODPPDWLRQ
LQWR D KLVWRSDWKRORJ\ VFRUH RQ D VFDOH RI WR
,PPXQRFKHPLFDO DQDO\VVH

)URJHQ FRORQ SLHFHV ZHUH KRPRJHQLJHG LQ D 3UHFHOO\V K
%UHWRRQQHX[)UDQFH LQ P0 7ULV ± P0 1D&O S+ 7KH C
DQG VXSHUQDWDQW ZDV VWRUHG DW f& XQWLO XVH ,/ DQG
\$/ 3HUNLQ (OPHU :DOWKDP 0\$ 86\$ \$&(VKHGGLQJ DQG FR
LQFXEDWLRQ VXSHUQDWDQWV DQG WLVVXH \$&(IURP O\VHG WLVV
6\VWHP 0LQQHV RWD 02 86\$ DQG &RUWLF RVWHURQH (,\$
\$QDO\WH FRQFHQWUDWLRQV ZHUH QRUPDOLJHG WR WRWDO SU
3LHUFHOE %&\$ 3URWHLQ \$VVD\ .LW 7KHUPR 6FLHQWLILF
5HYHUVH WUDQVFULSWDVH TXDQWLWDWLYH 3&5

&RORQ 51\$ ZDV H[WUDFWHG XVLQJ 1XFOHR6SLQ 51\$ 0DFKHUH
WUDQVFULEHG LQWR F'1\$ XVLQJ L6FULSWOE F'1\$ 6\QWKHVLV .LW
SHUIRUPHG LQ D /LJKW&\FOHUŠ ZLWK /LJKW&\FOHUŠ 6<%5
,QGLDQDSROLV ,1 86\$ \$OO SULPHUV ZHUH RUGHUHG IURP 6LJF
3ULPHU VHTXHQFH\$FWLZHUH ¶ &7*\$7**&&&\$**7&7*\$* ¶ 5
\$\$*7&\$*7*7\$&\$**&&\$*&6¶) ¶ \$\$&*\$&\$*7&7**&\$7 ¶ 5
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&\$&77\$7&7**7*\$7**& ¶ Q WR LQ HDFK JURXS LQ 57 T3&5 H

6WDWLVLWLFDO DQDO\VLV

7KH JHQH H[SUHVVLQR GDWD DUH SUHVHQWHG LQ WH[W DV UHOD
JHRPHWULF PHDQ LQ WKH ILJXUHV \$OO RWKHU GDWD DUH SUHV
LQGLYLGXDO GDWD SRLQWV DQG PHDQ 7KH GLIIHUHQFHV EHW
\$129\$ ZLWK 7SRHW\WKRFW RU .UXVND :DOOLV WHVW ZKHUH DSS
FRQGXFWHG E\ DGGLQJ QRLVH WR YDOXHV EHORZ WKH GHWHFW
DQG RXWOLHUV UHPRYHG LQ 7366XMHUVEREV WKDQG ZHUH FR
VLJQLILFDQW

5HVXOWV

0DFURVFRSLF VLJQV RI LQIODPPDWLRQ ZHUH QRW LPSURYHG E\
:H ILUVW FRPSDUHG ,9 DGPLQLVWHUHG DQG ,3 DGPLQLVWHUHG
)LJXUH \$ 06& WUHDWPHQWV KDG QR REYLRXV DGYHUVH HIIHF
LQGXFHG VLJQLILFDQW ZHLJKW OR(V,9 JURXS,9 JURXS3 JURXS
9(,3 JURXS)LJXUH \$ DQG FRORQ IRUDVHQLRQSV 7DEOH
JURXS FRPSDUHG ZLWK KHDOWK\ FRQWUROV 0DFURVFRSLF VFI
EORRG ZHUH VLJQLILFDQWO\ LQFUHDVHG FRPSDUHG ZLWK WKRV
,9 JURXS 06& ,3 JURXS 9(,3 JURXS H[FHSW LQ WKH 9(,9
LQ ZKLFK WZR PLFH KDG QRUPDO PDFURVFRSLF ILQGLQJ
PDFURVFRSLF VFRUHV ZHUH VLPLODU LQ WKH ,9 WUHDWHG DQG
UHVSHFWLYH YHKLFOH FRQWUROV)LJXUH \$ 7DEOH 7KHUH
ZHLJKW FRPSDUHG ZLWK ERG\ ZHLJKW EHWZHHQ DQ\ RI WKH JUR
WKH 06& ,9 JURXS WKDQ WKRVH IURP WKH RWKHU FROLWLVLV JURX

06&V UHGXFH WKH OHYHOV RI FRORQLF ,/ LQ DFXWH SKDVH RI
\$V WKHUH ZHUH QR VWDWLWVWLFDOO\ VLJQLILFDQW GLIIHUHQFHV
DGPLQLVWUDWLRQ URXWHV ZH PHDVXUH WKH FRQFHQWUDWLRQ
WKH FRORQV RI KHDOWK\ 06& ,9 DQG 9(,9 PLFH ,/ ZDV XQGH
)LJXUH & '66 FDXVHG DQ LQFUHDVH LQ ,/ FRQFHQWUDWLRQ
ZKLFK ZDV UHGXFHG E\ 06& WUHDWPHQWS XQGHWHF\WOBHOLVQZ
LQFUHDVHG LQ WKH 9(,9 JURXS FRPSDUHG ZLWK KHDOWK\ FRQW
S)LJXUH ' 7KHUH ZDV D WUHQG IRU ORZHU 71). FRQFHQ
SJ PJ FRPSDUHG ZLWK WKH 9(,9 JURXS EXW WKSH GLIIHUHQFH Z
6HYHULW\ RI FROLWLWV QRW LPSURYHG E\ 06&V LQ WKH UHJHQHU
:H QH[W FRPSDUHG WKH VDIHW\ DQG WKHUDSHXWLF HIILFDF\ RI
FROLWLWV PRGHO ZLWK D ORQJHU IROORZ XS WR VLPXODWH WKH
WKH FROLWLWV JURXSV VWDUWHG WR GHFOLQH DW GD\ RI '66 DQ
'66 FRQWURO DQG IUHVK 06& JURXSV DQG RQ GD\ FU\R 06&
ZHLJKW ZDV VLPLODU LQ DOO FROLWLWV JURXSV 7ZR PLFH LQ WK
06& DQG FU\R 06& JURXSV ZHUH VDFULILFHG GXH WR H[FHVZ
DQDO\VHV ILQDO Q LQ WKH IUHVK 06& DQG FU\R 06& JURXSV
OHQJWKV ZHUH UHGXFHG '66 FRQWURO JURXS DQG FU\R 06& JURXS
DQG FRORQ ZHSHJKWVIRQFDOO\WKH JURXSV LQ DOO FROLWLWV JUR
FRQWUROV 7KHUH ZHUH QR VWDWLWVWLFDOO\ VLJQLILFDQW GLII
VFRUHV ZHUH LQFUHDVHG '66 FRQWURO JURXS DQG FU\R 06& JURXS
IRU FRPSDUHG ZLWK WKH KHDOWK\ FRQWUROV 7DEOH)LJ
DQ\ VWDWLWVWLFDO GLIIHUHQFHV EHWZHHQ WKH FROLWLWV JURXS
LQILOWUDWLRQ LQ DOO FROLWLWV JURXSV)LJXUH % 6LPLOD
LQIODPPDWRU\ LQILOWUDWLRQ ZHUH LQFUHDVHG LQDOO FROL
JURXS DQG FU\R 06& JURXS FRPSDUHG ZLWK WKH KHDOWK\ FR

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VKHGGGLQJ LQ FRORQ PHDVXUHG DV UHOHDVHG \$&(SURWHLQ LQ
KHDOWK\ " QJ PJ DQG '66 FRQWURO " QJ PJ JU
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FRQWUROV 7KH UHGXFWRQ LQ \$&(VKHGGGLQJ E\ IUHVK 06&V
KHDOWK\ FRQWUROV ZDV SRW VWDWLWHDWPHQWUHQHMDQW E
FRPSDUHG ZLWK KHDOWK\ FRQWUROV, WKH IUHVK 06&V DQG FU
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'LVFXVVLQRQ

06&V KDYH WKHUDSHXWLF SRWHQWLDO LQ WKH WUHDWPHQW RI
PHGLFLQH +RZHYHU PXFK XQFHUWDLQW\ UHPDLQV LQ PDQIDF
LQ WKH WKHUDSHXWLF HIIHFW RI 06&V> @ 7KH UH
ZKLFK PLJKW EH GXH WR YDULDWLRQ LQ 06& VRXUFH FXOWXU
GLIIHUHQFHV LQ WKH DQLPDO PRGHQV XVHG LQ GLIIHUHQW VWXG
DOWHU WKH ELRGLVWULEXWLRQ RI 06&V DQG SRWHQWLDOO\
FU\RSUHVHUYHG RU IUHVK 06&V LV DOVR DVXEMHFW RI GLVSXW
FU\RSUHVHUYHG YDQLPDO PRGHQV> @ DQG WR WKH EHVW
FRPSDULVRQV EHWZHHQ GLIIHUHQW 06& SUHSDUDWLRQV LQ DQL
VWXG\ ZDV WR LQYHVWLJDWH WKH VDIHW\ SURILOH DQG IHDVLE
YHUVXV KRVW GLVHDVH> @ DQG WR FRPSDUH WKH LQIDPPDW
06&V DGPLQLVWHUHG HLWKHU ,9 RU ,3 LQ WKH '66 FROLWLQ PR
06&V VLQFH DOO FOLQLFDO WULDOV WKXV IDU KDYH XWLOLJHG

8QVWLPXODWHG PXULQH 06&V KDYH DOOHYLDWHG '66 LQGXFHG
UDQJLQJ IURP [FHOOV SHU LQMHFWRQ> @ +RZHYHU
QRW EHHQ HIIHFWLYH LQ [HQRJHQHLF FROLWLWV PRGHOV EXW SU
OLFHQVHG 06&V LQ [HQRWUDQVSODQWDWLRQ PRGHOV > @ 63
KDYH UHGXFHG LQWHVWLQDO GDPDJH LQ '66 DQG WULQLWUREH
DGGLWLRQ LQ D VWXG\ XWLOL]LQJ D UDGLDWLRQ LQGXFHG LQW
VKRZQ WR LQGXFH VHFUHWLRQ RI DQWL LQIODPPDWRU\ PHGLDW
OHVVHU GHJUHH RI PXFRVDO GDPDJH LQ 06& FRQGLWLRQHGH PHG
RI [XQOLFHQVHG KXPdq 06&V GLG QRW LPSURYH KLVWRSD
PDFURVFRSLF VFRUHV ,W LV SRVVLEOH WKDW OLFHQVLQJ RU D
HIIHFW RI KXPdq 06&V LQ D [HQRWUDQVSODQWDWLRQ PRGHO +R
RI FHOO PDQLSXODWLRQ DQG FRXOG SRVH DQ DGGLWLRQDO ULV
FOLQLFDO UHVXOWV WKXV IDU ERWK ZLWK SRVLWLYH DQG QHJ
06&V ,W LV SLRWDO WR LQYHVWLJDWH KXPdq FHOO SURGXFWV
EXW WKH WKHUDSHXWLF RXWFRPH LQ DQLPDO [HQRWUDQVSODQV
ZLWKRXW UHVHUYDWLRQV HVSHFLDOO\ LQ LQIODPPDWRU\ PRG
F\WRNLQHV VLP SO\ KDV OLWWOH RU QR UHDFWLYLW\ WRZDUG KX
VXSSUHVVLV 7KH VXLWDELOLW\ RI WKH '66 PRGHO LQ VWXG\LQ
UHJDUGV WR KXPdq ,%' KDV EHHQ FULWLFL]HG DV WKH LQIODP
LPPXQLW\ DQG QRW 7 FHOOV ZKLFK DUH LPSRUWDQW LQ ,%' SD
WKH DELOLW\ WR SRODUL]H PDFURSKDJHV ZKLFK DUH DEXQGDQ
WR DQWL LQIODPPDWRU\ 0 PDFURSKDJHV ZKLFK SURPRWH WLW
SRODULJDWLRQ> @ 1RQHWKH OHVV UHVXOWV IURP FOLQLFDO
GHULYHG 06&V LQGLFDWH WKDW WKH\ FDQ EH HIIHFWLYH LQ W
UHFUXUULQJ V\VWHPLF LQIXVLQV> @ RU ORFDO DGPLQLVWUDWL
06&V KDYH EHHQ DGPLQLVWHUHG LQ SDWLHQWV HLWKHU E\ OR
LQIXVLQV> @ *RQFDOYHV HW DO > @ UHSRUWHG WKDW ,9

HIIHFWV WKDQ ,3 LQMHFWHG 06&V ZKHUHDV LQ RWKHU VWXGLH
DGPLQLVWHUHG 06&V> @ ,Q RXU VWXG\ ZH IRXQG QR VWDV
DGPLQLVWUDWLRQ URXWHV 1HYHUWKHOHVV ,9 DGPLQLVWUDWL
WR ERG\ ZHLJKW ZKLFK ZDV ORZHU LQ WKH 06& ,9 JURXS LQGLF
FOLQLFDO VWXGLHV WKH VDIHW\ SURILOH RI 06&V LV GHHPHG V
,9 DGPLQLVWHUHG 06&V DUH SURPLQHQWO\ UHWDLQHG LQ WKH
FLUFXODWLRQ> @ ,Q RXU VWXG\ ZH UHSRUW WKDW ERV
REYLRXV DGYHUVH HIIHFWV H J LQIHFWLRQV RU HPEROL ZHU
DGPLQLVWUDWLRQ URXWH LV FOLQLFDOO\ PRUH IHDVLEOH ZH F
7KHUH DUH UHSRUWV LPSO\LQJ WKDW FU\RSUHVHUYHGDV\RSU
@ EXW FU\RSUHVHUYHG 06&V KDYH EHHQ H[SORUHG LQ VHYH
XV DQG RWKHUV ZLWK SDUWLDOO\ HQFRXUDJLQJ UHVXOWV>
IUHVK QRU FU\RSUHVHUYHG 06&V LPSURYHG WKH FROLWLW LQ W
DQG PDFURVFRSLF RU KLVWRSDWKORJ\ VFRUHV RU E\ FRORQLF
:KLOH 06&V SUHYHQWHG WKH '66 LQGXFHG XSUHJXODWLRQ RI W
SKDVH RI FROLWLW LQGLFDWLQJ D PLOG DQWL LQIODPPDWRU\ H
UHJHQHUDWLYH SKDVH 7KH SRVVLEOH WKHUDSHXWLF GLIIHUHQ
XQVROYHG LQ WKLV VWXG\ VLQFH WKH RYHUDOO PLQLPDO WKHU
DOVR QRWHZRUK\ WKDW WKH ORVV DQG VXEVHTXHGW GDWD I
HVSHFLDOO\ LQ WKH '66 FRQWURO JURXS LQ '66 FRQWURO JU
GLIIHUHQFHV LQ WKH GDWD VHW

5HFHQW ILQGLQJV LQ H[SHULPHQWDO PRGHV VXJJHVV WKDW V
LQWHVWLQDO LQIODPPDWLRQ> @ 5\$6 LV D FULWLFDO UHJXOD
WKURXJKRXW WKH LQWHVWLQH 7KH NH\ HQJ\PH RI 5\$6 DQJLRWH
, WR DQJLRWHQVLQ ,, DQG LW LV SURPLQHQWO\ H[SUHVHG LQ
PRGHV DFWLYDWLRQ RI 5\$6 SURPRWHV FROLWLW> @ ZKLOH 5\$
@ &OLQLFDO VWXGLHV KDYH VKRZQ WKDW DQJLRWHQVLQ , DQ

&URKQ¶V GLVHDTVH SDWLHQWV ZLWK DFWLYH LQIODPPDWLRQ> @
SRO\PRUSKLVVPV LQ WKH \$&(JHQH> @ 'HVSLWH DFFXPXODWLQJ
PRGXODWLRQ LQ H[SHULPHQWDO FROLWLV WKH IXQFWLRQV RI L
KHDOWK DQG GLVHDTVH

,Q WKL V WXG\ ZH LQYHVWLJDWHG KRZ 06&V LQWHUDEFW ZLWK L
HFWRGRPD LQ VKHGGLQJ LQ WKH FRORQ DUH GRZQUHJXODWHG E
\$&(VKHGGLQJ LV HQKDQFHG E\ LQIODPPDWLRQ LQ FHUWDLQ SD
FRORQ> @DQG XQSXEOLVKHG REVHUYDWLRQV@ ,Q SUR[LPD
LWVHOI EXW FRXOG EH UHGXFHG E\ \$&(LQKLELWLQJ DJHQWV> @
FU\SW FHOOV RU FOHDYHG E\ D VSHFLILF VKHGGDVH '\$\$0 > @
LQWHVWLQH LV QRW NQRZQ EXW VLQFH \$&(LV FRQVLGHUHG SU
OHYHOV E\ 06&V PLJKW EH D EHQHILFLDO UHVSRQVH WR UHGXFH
\$&(\$QJ , , \$*7 5\$JWUHV SUHVVLQJ LV LQGXFHG LQ LQIODPPDWLRQ\
YDVFXODWXUH> @ DQG LQ WKH JDVWULF PXFRVD> @ 'RZQUH
LQIODPPDWLRQ DQG WLVVXH KHDOLQJ PLJKW LQGLFDWH D QHJD
DQJLRWHQVLQ , , OHYHOV SUHVVLQJ LQ WKH WLVVXH UHJHQ
'66 LQVXOW KDG SDVWUHQGLQJ WKH WKDWLJQLILFDQWO\ GRZQU
DQLPDOV 7KHUH ZDV D VPDOO EXW QRW VWDWLVWLSDOHVLRQQL
WKH 06& WUHDWHG DQLPDOV ,QWHUHVWLQJO\ LQ VWXGLHV RI
XSUHJXODWLRQ RI \$&(DQG \$*7 5 SURWHLQ DQG P51\$ H[SUHVVLR
WKL V WXG\ GHPRQVWUDWHV WKDW 06&V UHJXODWH LQWHVWLQD
DUH SDUWO\ IDFLOLWDWHG YLD WDUJHW WLVVXH 5\$6 VKRXOG EH

&RQFOXVLRQV

:H HYDOXDWHG IUHVK DQG FU\RSUHVHUYHG XQOLFHQVHG SODW
SUHFOLQLFDO PRXVH PRGHO GXULQJ ERWK WKH DFXWH DQG W
PLFURVFRSLF DQG PROHFXODU SDUDPHWHUV UHYHDOHG QR DG

VDIHW\ SURILOH RI V\VWHPLFDOO\ DGPLQLVWHUHG 06&V ,Q WKL
XQOLFHQVHG KXPdq 06&V L H VXFk DV WKH\ DUH XWLOLJHG LQ
WKH OHYHOV RI SUR LQIODPPDWRU\ F\WRNLQHV &RORQLF ,/
LQIODPPDWLRQ EXW D EHQHILFLDO HIIHFw ZDV QRW DV HYLGH
WRJHWKHU WKLv PLJKW LQGLFDWH WKDW WKH IXOO DQWL LQIO
[HQRWUDQVSODQWDWLRQ PRGHO PHGLDWHG PDLQO\ E\ WKH
[HQRWUDQVSODQWDWLRQ PRGHO VKRXOG QRW EH H[WUDSRODWH
FRQFOXGH WKDW 06&V UHJXODWH LQWHVWLQDO 5\$6 E\ UHGXF
HFWRGRPDLQ VKHGGLQJ LQ WKH FRORQ ZKLfk PLJKW LPSOLF
E\ 06&V \$GGLWLRQDO VWXGLHV XVLQJ XQOLFHQVHG YHUVXV OL
YHULI\ WKH RSWLPDO PDQXIDFWXULQJ VWUDWHJLHV IRU WKH EH

/LVW RI DEEUHYLDWLRQV

\$&(\$QJLRWHQVLQ FRQYHQRQDQJLHV WUDQ VRGLXP+VXODV\HOLQ
DQG H\VLQUDIW YHUVXV,%R\QOGLPDDWRU\ ERZQUGLSHULWHRQHD
,QWUDYHQRXVHQFK\PDO &WURPDQ\RSOQVHUYHIGV6608
FXOWLYDWHSHQ&Q DQJLRWHQVLQ V\VWHP

'HFODUDWLRQV

(WKLFV DSSURYDO

7KH DQLPDO H[SHULPHQWV ZHUH DSSURYHG E\ WKH QDWLR
(6\$9, DQG (6\$9, DFFRUGLQJ WR W
([SHULPHQWDWLRQ

&RQVHQW IRU SXEOLFDFWLRQ

1RW DSSOLFDEOH

\$YDLODELOLW\ RI GDWD DQG PDWHULDQV

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