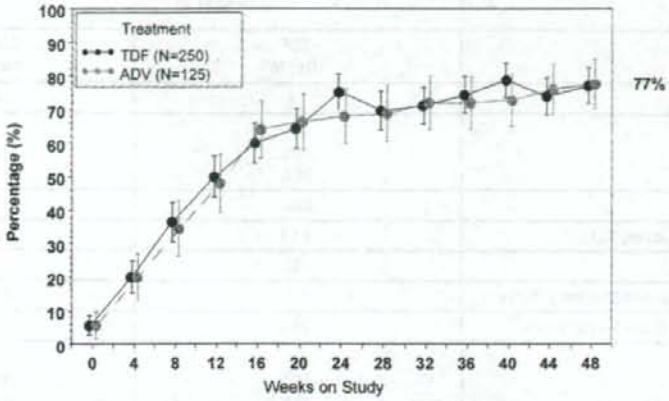

図4　ALTの正常化に至った症例比率
(Missing=Failure)

表2　グレード3/4の臨床検査値異常

Test Name	TDF (N=250)	ADV (N=125)
At least one G3/G4	12.4%	11.2%
Serum amylase ↑	3.6%	1.6%
Serum lipase ↑	0.8%	0.8%
ALT (SGPT) ↑	4.0%	2.4%
AST (SGOT) ↑	2.4%	3.2%
Confirmed ↓ phosphorus < 2mg/dL	1.6%	0%
Confirmed 0.5 mg/dL ↑ in creatinine	0%	0%

かった。また，グレード3/4の臨床検査値異常についても両群間で明らかな差は認められなかった（表2）。TDF群においてクレアチニン0.5 mg/dL以上の増加やクレアチニンクリアランス＜50 mL/minを示す症例は認められなかった。ALTの再燃（>10倍×基準値上限，ベースライン時の値の2倍と定義）については，両群とも低く，同程度であった（1.2％ vs 0.8％）。

以上より，HBe抗原陰性のHBV単独感染患者において，TDFは忍容性が良く，ADVより優れた効果を有することが示された。

2．HBe抗原陽性のHBV単独感染患者におけるTDFの抗HBV作用（Study GS-US-174-0103；103試験）[3]

本試験は，未治療のHBV単独感染患者（HBe抗原陽性）266例を対象に，TDF 300mgの1日1回投与（以下，TDF群。N=176）とADV 10mgの1日1回投与（以下，ADV群。N=90）を比較した多施設二重盲検の無作為化コントロール試験である。主要評価項目としては，102試験と同様に，肝線維化の悪化を伴わず，投与後48週に

表3　ベースライン時の患者背景

	TDF (N=176)	ADV (N=90)
Mean Age	34	34
Race		
White	52%	51%
Asian	36%	36%
Male	68%	71%
Mean HBV (log_{10} copies/mL)	8.64	8.88
Mean ALT (IU/mL)	142	155
Mean Knodell Necroinflammatory Score	8.3	8.5
Knodell Fibrosis Score = 4 (cirrhosis)	20%	21%
Genotype		
A	24%	21%
B	15%	11%
C	25%	30%
D	32%	35%

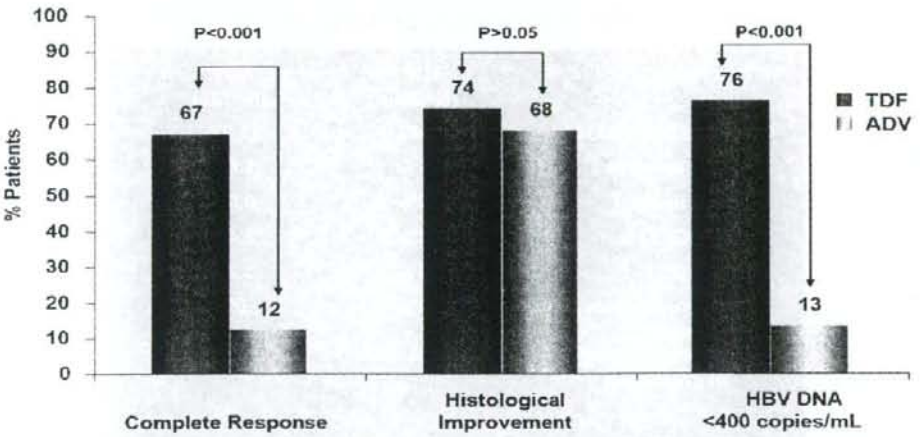

図5　103試験　主要評価項目および副次的評価項目

完全寛解（血清HBV DNA<400 copies/mL，かつ組織学的改善：Knodell壊死性炎症スコア2ポイント以上の低下）に至った症例比率である。

ベースライン時の患者背景は，両群ともに同様であった（表3）。平均HBV DNA量はTDF群8.64 log_{10} copies/mL，ADV群8.88 log_{10} copies/mLであり，平均ALT値はTDF群142 U/L，ADV群155 U/Lであった。Knodell壊死性炎症スコアはTDF群8.3，ADV群8.5であり，両群ともに約20％が肝硬変を有していた。

投与後48週において完全寛解に至った症例の比率は，TDF群は67％であり，ADV群の12％に比較して，有意に高率であった（p<0.001，図5）。また，HBV DNA<400 copies/mLに至った症例の比率は，TDF群が76％であり，ADV群の13％に比較して，有意に高率であった（p<0.001，図5，図6）。一方，組織学的改善においては，両群で明らかな差は認められなかった（74％ vs 68％，p>0.05，図5）。平均HBV DNA量の減少の推移では，TDF群は102試験の場合と同様に減

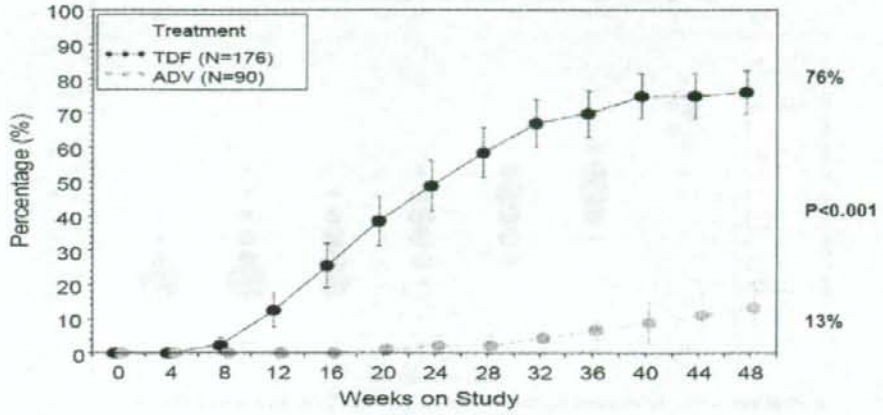

図6　HBV DNA<400 copies/mLに至った症例比率（Missing=Failure）

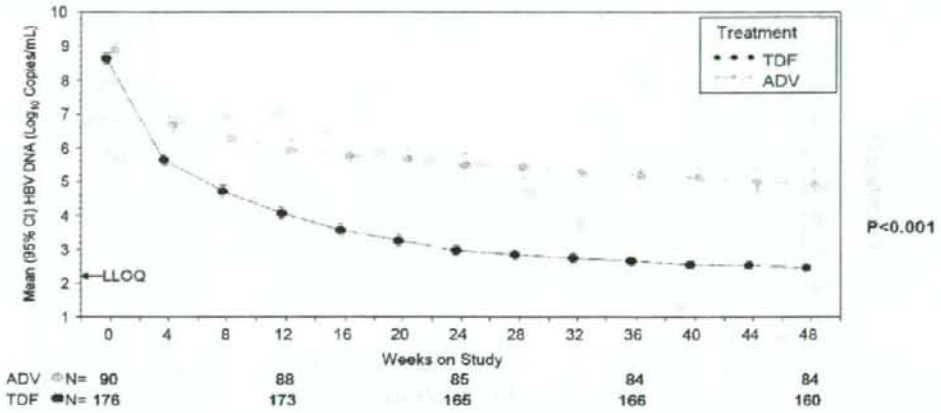

図7　平均HBV DNA量の推移

少の程度は大きかったが，ADV群は102試験と比べて減少の程度が小さく，両群間で有意差が認められた（p<0.001，図7）。TDF群のHBVのクリアランスの推移として，ベースライン時から48週までの各時点において，HBV DNA量毎の患者分布の推移をみたところ，8週時点でHBV DNA量が検出限界未満に至った症例を認め，24週以降ではTDF群の多くの症例が検出限界未満に至っていた（図8）。また，ALTの正常化を示した症例比率は，TDF群が69％であり，ADV群の54％に比較して，有意に高率であった（p=0.018，図9）。図10に投与後48週のHBeおよびHBsセロコンバージョンの比率を示した。TDF群におけるHBeセロコンバージョン率は20.9％であり，ADV群の17.5％と比較して，明らかな差はなかった（p>0.05）。一方，HBsセロコンバージョンについては，ウイルスが排除された状態を示唆する「HBs抗原の消失」に至った症例は，ADV群の0％に対し，TDF群では3.2％と有意な高値（p=0.018）であったが，過

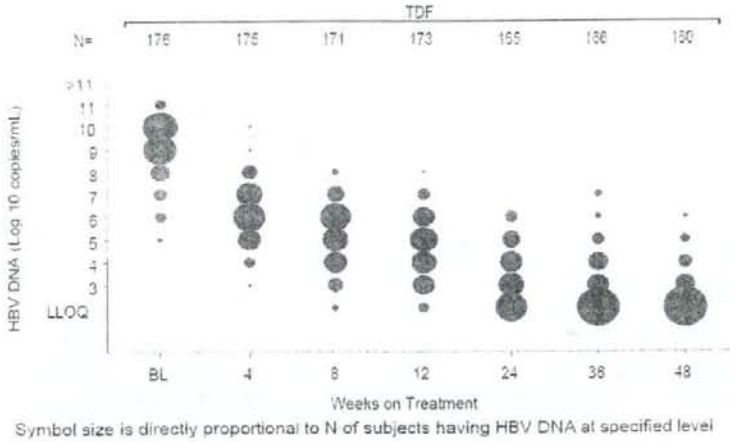

図8　TDF群におけるHBV DNA量のクリアランス

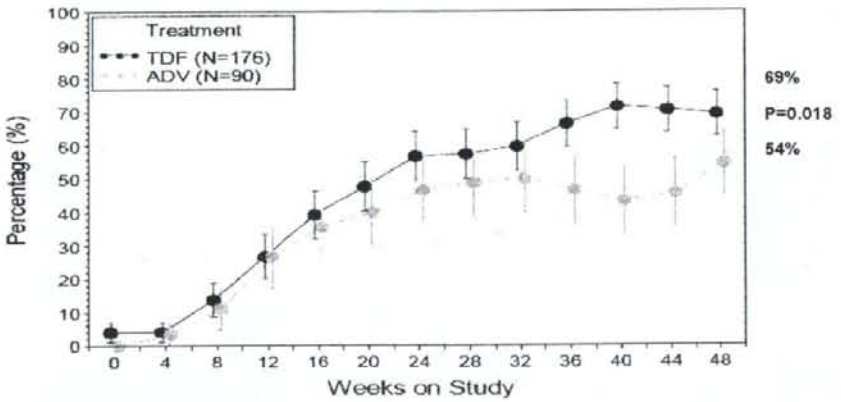

図9　ALTの正常化に至った症例比率（Missing=Failure）

去のHBV感染を示す「HBs抗体の出現」まで至った症例は，TDF群で1.3％であった（p>0.05）。

投与後48週時にTDF群においてHBV DNA≧400 copies/mLであった症例について耐性検査を実施したが，TDF耐性にかかわる変異はみられなかった。

本試験における安全性については，グレード2-4の有害事象は両群間で明らかな差を認めなかった（表4）。また，グレード3/4の臨床検査値異常についても両群間で明らかな差は認められなかった。TDF群においてクレアチニン0.5 mg/dL以上の増加やクレアチニンクリアランス＜50 mL/minを示す症例は認められなかった。ALTの再燃（>5倍×基準値上限，ベースライン時の値の2倍と定義）については，TDF群は11.4％であったのに対し，ADV群は4.4％であった。このALT再燃は，主として，投与開始から最初の8週以内に，HBV DNA量が大きく減少

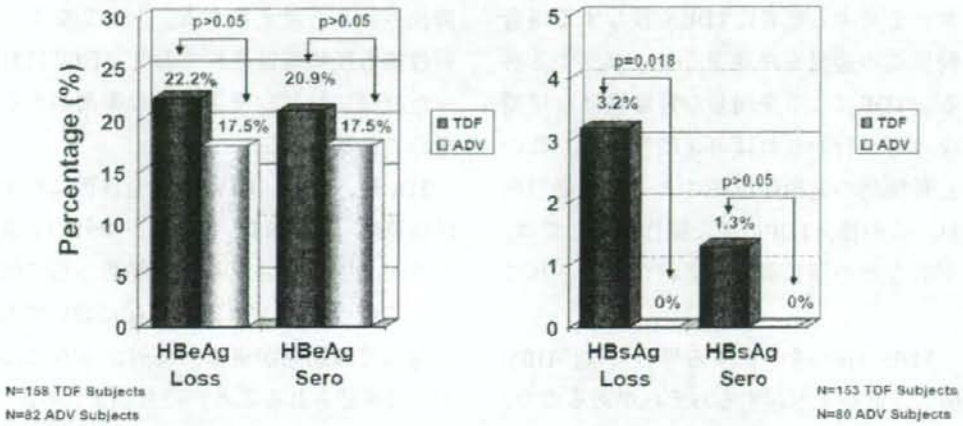

図10　投与後48週におけるHBeセロコンバージョンおよびHBsセロコンバージョン

表4　有害事象および臨床検査値異常

	TDF (N=176)	ADV (N=90)
Adverse Event, % subjects with:		
Grade 2,3,4 AE	31%	32%
SAE	8.5%	7.8%
AE that resulted in DC	0	1.1%
Laboratory Abnormality, % subjects with:		
G3/4 (ALT >5 x ULN) and > 2 x Baseline	11.4%	4.4%
G4 (ALT >10 x ULN) and > 2 x Baseline	4.5%	3.3%
Confirmed 0.5 mg/dL increase in creatinine	0	1%

したことに関連していた。

以上より，HBe抗原陽性のHBV単独感染患者において，TDFは忍容性が良く，ADVより優れた効果を有することが示された。

3．TDFの安全性

概説した2試験の安全性については各試験毎に記載したが，これらの試験において，TDFの安全性はADVと同様であり，忍容性が高いことが示された。これまでに報告されているHIV/HBV合併例におけるTDFの使用経験においても，特記すべき重篤な副作用は報告されていない。また，TDF投与中，ALTの上昇を示した症例が認められているが，肝不全に至った症例はない。

TDFの最も注意すべき副作用として，腎障害がHIV感染症患者で報告されているが，今回の2試験を含め，これまでHBV単独感染患者において腎機能の明らかな変動の報告はない。これまでの発現例の多くでは，他の腎障害のリスクファクターを有していたことが報告されている。従って，腎毒性を有する薬剤との併用，腎疾患の既往，あるいは糖尿病の合併等，他にリスク

ファクターを有する患者にTDFを投与する場合には，腎機能の経過を注意深くフォローする必要がある。TDFにより発現した腎障害は，早期に適切な対応が行われれば可逆的であり，この意味でも腎機能の定期的なモニターは重要である。なお，この他，TDFの主な副作用としては，鼓腸，下痢などの消化器系の症状が報告されている。

また，TDFの投与を中断する場合には，HBVが再増殖し，肝炎を惹起するおそれがあるので，十分注意が必要である。特に，非代償性肝硬変例の場合，重症化するおそれがあるので注意が望まれる。

おわりに

現在，本邦におけるB型慢性肝炎に対する抗ウイルス薬としてインターフェロンとLAM，ADVおよびETVの4剤が使用可能である。B型慢性肝炎に対する治療方針はHBe抗原の有無や患者の年齢によって大きく異なるが，核酸アナログを長期投与する際には，薬剤耐性株の出現について注意が必要である。LAM耐性株の出現によって，肝炎が再燃する例が問題であったが，ADVの併用やETVの使用が可能となり，多くは解決されると考えられる。しかしながら，ETV耐性株も既に報告されており，ETVに耐性となった症例に対し，使用可能な薬剤があることは極めて重要である。

TDFは，既に，HIV/HBV合併例に対する多剤併用療法（HAART）として，海外の主要なガイドラインで選択されるべき薬剤として位置付けられている。HBV単独感染症においても，TDFの海外での開発が進み，海外，さらには本邦において承認されることが待ち望まれる。

文献

1) Lok AS and McMahon BJ, Chronic Hepatits B. Hepatology. :45(2):507-539, 2007.

2) Maecellin P, Buti M, Krastev Z, *et al.*: A randomized, double-blind, comparison of Tenofovir DF(TDF) versus Adefovir Dipivoxil(ADV) for the treatment of HbeAg-negative chronic hepatitis B(CHB):Study GS-US-174-0102. AASLD Novenber 2-6, Abst. LB2, 2007.

3) Heathcote J, Gane E, DeMan R, *et al.*: A randomized, double-blind, comparison of Tenofovir DF(TDF) versus Adefovir Dipivoxil(ADV) for the treatment of HbeAg positive chronic hepatitis B(CHB):Study GS-US-174-0103. AASLD Novenber 2-6, Abst. LB6, 2007.

☆　☆　☆　☆

日消誌 2008：105：199—205

今月のテーマ●ウイルス性肝炎の最新治療

B型肝炎ウイルスの変異と治療

四柳 宏 小池和彦[1]

要旨：B型肝炎ウイルス遺伝子の変異をopen reading flame毎に概説した．preS-S領域においてはvaccine-induced escape mutant．PreS2領域の大きな欠失などが見られる．また，preC-C領域においてはHBe抗原の産生を低下させるプレコア領域および上流のbasic core promoter領域の変異が知られており，劇症肝炎や肝細胞癌との関連が示唆される．また，P領域の変異は各種核酸アナログ製剤の耐性株出現時に見られる変異である．

索引用語：vacccine-induced escape mutant，Occult HBV感染，HBe抗原，核酸アナログ

B型肝炎ウイルスは，その増殖の過程にRNAからDNAへの逆転写を含む．このため，他のDNAウイルスに比較してウイルス遺伝子の変異の頻度が高い．

遺伝子の変化がウイルス蛋白のプロモーター領域を始めとする転写調節領域に遺伝子変異がおきるとウイルス蛋白の発現量が変化する．また，アミノ酸変異により，ウイルス蛋白の読み取り枠（open reading flame：ORF）に変化がおこると，生成される蛋白の立体構造や抗原性に変化がおきる．こうした遺伝子あるいはアミノ酸の変異は，B型肝炎の病態や治療効果に影響を及ぼすことが知られている．ここではB型肝炎ウイルスのORF毎に遺伝子/アミノ酸変異に関して述べる．

I preS-S領域の変異

1. Vaccine-induced escape mutant

S遺伝子はHBVのエンベロープであるHBs抗原をコードする遺伝子である．HBs抗原の抗原性を決定するのに最も大切なのは"a determinant region"（AA124-147）と呼ばれる領域である．

この領域はS遺伝子の親水性領域である"major hydrophilic region（MHR）"（AA99-169）に含まれ，HBVの表面から突出する2つのループを作る（Figure 1）．したがってこの領域にアミノ酸変異がおきた場合，HBs抗原の構造に変化がおこる可能性がある．その代表が"vaccine-induced escape mutant"である．この変異株は，母子感染防止のためにHBワクチンの接種を受けた児の中に，HBs抗体陽性にもかかわらずHBs抗原陽性の例が見られたことからその存在が明らかにされた．最も有名なものはS遺伝子の145番目のアミノ酸（"a determinant region"内の2番目のループ上に位置する）がグリシンからアルギニンに置換された変異（G145R）である[1]．この変異があるとHBワクチンで誘導されたHBs抗体とHBs抗原との結合力が低下することが確認されている．G145Rが検出された児の母親からはG145Rが検出されないことから，G145Rはワクチン投与によって誘導されたものであると考えられる．

145番目のアミノ酸以外では，126番目，129番目，141番目にアミノ酸置換を有するものが

1）東京大学医学部・生態防御感染症学

Mutations in the hepatitis B virus and treatment of hepatitis

Hiroshi YOTSUYANAGI and Kazuhiko KOIKE[1]

1）Department of Infection Control and Prevention, Division of Microbiology Graduate School of Medicine and Faculty of Medicine, University of Tokyo

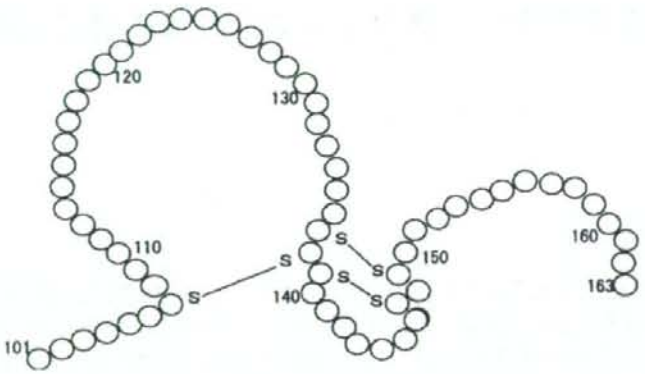

Figure 1. S遺伝子内の "a determinant" の構造

"vaccine-induced escape mutant" としてよく知られている[2)3)].

2. PreS1 および PreS2 領域の変異

S 領域の上流にはこれら2つの領域があり，S 抗原には PreS1 から S までを含む "Large S protein"，PreS2 から S までを含む "Middle S protein"，S のみから生成される "Small S protein" の3種類がある．PreS1 領域の N 末端には，肝細胞表面への付着に必要な部位がある．また，C 末端には S promoter が存在する．したがって PreS1 領域はウイルスの増殖にとって大切な領域であり，変異は限られた部位にしか認められない[4)]．

PreS2 領域は，開始コドン部位に欠失や変異の入った株や大きな欠失を有する株が分離されている[4)]．したがってウイルスの増殖や感染には必要不可欠な部位ではない．PreS2 領域の欠失は，B cell epitope や T cell epitope を消失させ，ウイルスに対する免疫応答を減弱させることから，ウイルスが生体の免疫応答から逃れるために変異したものと考えられる．

PreS2 領域の欠失は進展慢性肝疾患に多いことが最近台湾からの大規模な検討で明らかにされている[5)6)]．preS2/S 蛋白は肝組織への組み込みから肝発癌へ関与している可能性が以前から指摘されており，関連のある可能性もある[7)]．

3. HBs 抗原陰性慢性肝疾患の症例における S 遺伝子変異

血清 HBs 抗原が陰性でありながら，HBV DNA が検出される症例は "Occult HBV 感染" と呼ばれる．HBV の変異により HBs 抗原の立体構造の変化がおこり，現行の検査では検出できない場合，HBs 抗原は見かけ上陰性となる場合がある[8)~10)]．また，HBV の複製や HBs 抗原の翻訳を阻害するような変異が生じた場合にも HBs 抗原は陰性となり得る[11)~13)]．

II preC-C 領域の変異

1. プレコア領域（precore PreC：nt1814-1901）の変異

この領域の変異として最もよく知られているのは，nt1896 が G から A に変化することにより，28番目のアミノ酸がトリプトファン（TGG）から停止コドン（TAG）へと変化する変異である．この変異により，HBe 抗原の産生，分泌が不能となる．

Nt1896 の変異は HBe 抗体陽性の無症候性キャリアおよび慢性活動性肝炎患者で見られることが当初報告されたが[14)15)]，その後，劇症肝炎患者でこの変異が高率に認められることが報告された[16)17)]．

Nt1896 の他には nt1899 などに変異をともなうことがある．

2. コアプロモーター領域（basic core promoter BCP：nt1742-1849）の変異

BCP領域はHBe抗原・コア蛋白質のmRNAの転写を制御する領域である．nt1762，nt1764の変異（nt1762 A→T，nt1764 G→A）により転写因子の結合が阻害され，プロモーター活性に影響が生じ，プレゲノムRNAの転写効率が亢進する．したがってウイルスの増殖は活発になる．また，nt1762，nt1764の変異によりpreC mRNAの翻訳は抑制され，結果的にHBe抗原の産生は低下する．

nt1762/1764の変異もpreC領域の変異同様劇症肝炎で高率に認められることが報告された[18][19]．

nt1762/1764の変異によりウイルス増殖能は約2倍に増加するが，さらにnt1753，nt1766，nt1768に変異が入った場合，ウイルスの増殖能は約8倍となる[20]．

HBe抗原の役割の1つは免疫応答の調節への関与だと考えられており，HBe抗原量が低下することにより，肝炎の病勢が強くなることが考えられる．B型急性肝炎では，変異型ウイルス（preCあるいはBCPの変異）の感染により，重症化・劇症化しやすいことが報告されている．しかしながら，上述のようにこれらの変異はHBe抗体陽性の無症候性キャリアでも見られることがわかっており，これらの変異のみで肝炎の重症化を説明するのは困難である．

3. preCおよびBCP領域の変異と慢性肝炎

preC領域nt1896およびBCP領域nt1762/1764の変異は慢性肝炎の自然経過とも密接な関連がある．

nt1896の変異はGenotype Bの症例ではGenotype Cの症例に比較して早期に検出されることが多い．nt1896が変異型，nt1762/1764が野生型の症例はGenotype Bで多く見られるが，この場合肝炎が早期に沈静化し，HBe抗体陽性の無症候性キャリアへと移行していくことが多い[21]．

Genotype Cの症例の多くでは，nt1762/1764の変異が早期におこり，nt1896の変異は遅れて出現する．nt1762/1764が変異型（nt1762 A→T，nt1764 G→A），nt1896が野生型の場合，ウイルスの増殖は旺盛で，肝病変の進展は速い．HBe抗原は陽性の場合が多い．nt1896が変異型になると肝炎は少しずつ沈静化に向かう[22]．

したがってBCP変異（nt1762 A→T，nt1764 G→A）は肝障害の程度と持続期間を反映し，preC変異（nt1896 G→A）は肝炎の沈静化を反映すると考えられる．したがって，肝炎増悪期にウイルス変異の各型を調べることで，抗ウイルス治療を行うかどうかの目安とすることが可能である．

なお，インターフェロン治療効果とBCP変異との間にも関連があるとされている[23][24]．

4. preCおよびBCP領域の変異と肝細胞癌

肝細胞癌の症例の大多数にはBCP変異（nt1762 A→T，nt1764 G→A）が認められる[25][26]．しかし，前述の通り無症候性キャリアにもこの変異は認められることを考えると，BCP変異は肝細胞癌発生のための必要条件に近いものと考えられる．

BCPおよびその上流の配列（転写調節に関与している）はX領域とoverlapすることもあり，発癌との関連がある可能性がある．本邦における解析からは，Genotype CのHBVキャリアの発癌例においては，非発癌例に比べ，1653番目および1753番目の変異が高率に認められることが示唆されている[27]．

5. コア領域の変異と慢性肝炎

HBe抗原陽性の症例の場合，無症候性キャリアに比べ，慢性肝炎例ではコア領域のアミノ酸変異が高率に認められる．特にAA84-101は超可変領域（hypervariable region）と呼ばれ，変異が集積している[28]．

これに対し，HBe抗体陽性の場合，慢性肝炎例に比較し，無症候性キャリアでコア領域のアミノ酸変異が高率に認められることが示唆されている[29]．

III ポリメラーゼ（pol）領域の変異

HBV pol遺伝子は（Figure 2）のような構造をしている．このうち，Pol/RT領域はHBVの逆転写酵素（reverse transcriptase）をコードする領域である．HBVはウイルス遺伝子の複製の際に，pregenomic RNAからウイルス遺伝子である

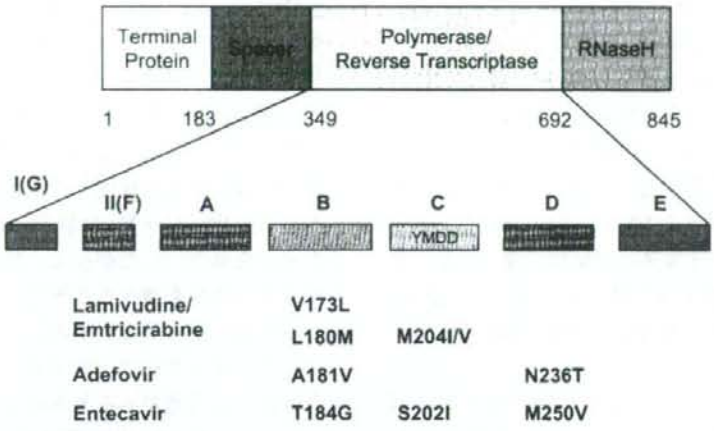

Figure 2. HBV ポリメラーゼ遺伝子の構造

Durantel D et al. J Clin Virol 2005 より

DNA への逆転写がおこる．この際に使われるのが逆転写酵素である．Pol/RT 領域はさらに Domain A から Domain E までの5ドメインに分かれている．Domain C には Pol/RT の活性中心があるとされている．Domain B，E は RNA テンプレートの結合に，Domain A，D は核酸との結合にそれぞれ重要とされている．

核酸アナログ製剤は逆転写の際に核酸の代わりに取り込まれてウイルスの複製を競合阻害するため，Pol/RT 遺伝子に変異が入った場合には薬剤耐性となる可能性がある．

主な核酸アナログ製剤に対し，耐性をもたらす，Pol/RT 遺伝子の変異を（Figure 2）に示す．

1．ラミブジン（LAM）に対する耐性

LAM 耐性の原因となるのは，Polymerase 領域の 204 番目のメチオニンがバリンあるいはイソロイシンに置換される変異（rtM204V/I）であり，YVDD 変異/YIDD 変異とも呼ばれる．また，rtM 204V/I に随伴する変異として，180 番目のロイシンがメチオニンに置換される変異（rtL180M）が知られている．

rtM204M は HBe 抗原陽性 B 型慢性肝炎の場合，投与 24 週後で 10%，52 週後で 24%，5 年後で 65% に出現したと報告されている[30]．本邦における長期成績として，HBe 抗原陽性，陰性いずれの場合も投与5年後で 50% の耐性株出現率と報告されている[31]．

rtM204M を有する例のすべてに肝炎をともなうわけではない．肝炎のある症例ではポリメラーゼ遺伝子のアミノ酸変異が多いという報告があるものの，一定の変異が認められるわけではない．

最近，YMDD motif に変異がないにもかかわらず，LAM に耐性の症例が報告された．この症例では Pol 領域の 181 番目のアラニンがスレオニンに置換されており（rtA181T），キメラマウスを用いた実験により，この変異は LAM 耐性をもたらすことが証明されている[32]．

2．アデフォビル（adefovir dipivoxil）に対する耐性

Adefovir dipivoxil（ADV）は本邦ではラミブジン耐性が出現した症例に対し，ラミブジンとの併用で使用が許可されている．

ADV に対する耐性ウイルスの出現は，当初 ADV 単剤で検討が行われた．投与開始後3年で約 6% の症例に耐性が出現したと報告されている．耐性株には Pol 領域の 236 番目のアスパラギンのスレオニンへの置換（rtN236T），181 番目のアラニンのバリンへの置換（rtA181V），が認められている[33]．

一方，LAM 耐性が出現した症例に対し ade-

fovir dipivoxil (ADF) を投与した場合，投与開始後1年で18%の症例にrtA181V/TあるいはrtN236Tが出現したと報告されている[34]．rtA181TはYMDD motif内の変異を欠くLAM変異株にも認められる変異である．また，LAM耐性が出現した症例の中にはADVが最初から無効の症例があることが最近報告されたが，この場合rtI233Vを持つ株であることが確認されている[35]．しかしながら，LAM耐性例に対しては，ADF単独療法ではなく，ADFとLAMの併用を行うことで，ADF耐性株の出現は極めて低率に抑えることが可能である[36]．

3. エンテカビル (entecavir：ETV) に対する耐性

ETVを核酸アナログの治療歴のないB型慢性肝炎に対して使用した場合，ETV耐性となる頻度は極めて低いが[37]，LAM耐性例に使用すると48週投与で32%の症例に耐性ウイルスが出現したとする報告がある[38]．耐性ウイルスのRT領域のアミノ酸配列は2症例で解析されており，1症例ではrtM250V，rt169Tが，もう1症例ではrtT184GおよびrtS202Iが認められている[39]．また，本邦からはrtS202G，rtL269Iが報告されている[39]．ETV耐性を獲得した症例は現在までのところ，いずれもLAM耐性の症例であるが，ETV単独で治療を開始した場合の薬剤耐性ウイルスの出現については今後検討が必要である．

文　献

1) Carman WF, Zanetti AR, Karayiannis P, et al: Vaccine-induced escape mutant of hepatitis B virus. Lancet 336: 325-329: 1990
2) Okamoto H, Yano K, Nozaki Y, et al: Mutations within the S gene of hepatitis B virus transmitted from mothers to babies immunized with hepatitis B immune globulin and vaccine. Pediatr Res 32: 264-268: 1992
3) Chiou HL, Lee TS, Kuo J, et al: Altered antigenicity of 'a' determinant variants of hepatitis B virus. J Gen Virol 78: 2639-2645: 1997
4) Kay A, Zoulim F: Hepatitis B virus genetic variability and evolution. Virus Res 127: 164-176: 2007
5) Chen BF, Liu CJ, Jow GM, et al: High prevalence and mapping of pre-S deletion in hepatitis B virus carriers with progressive liver diseases. Gastroenterology 130: 1153-1168: 2006
6) Chen CH, Hung CH, Lee CM, et al: Pre-S deletion and complex mutations of hepatitis B virus related to advanced liver disease in HBeAg-negative patients. Gastroenterology 133: 1466-1474: 2007
7) Kekulé AS, Lauer U, Meyer M, et al: The preS2/S region of integrated hepatitis B virus DNA encodes a transcriptional transactivator. Nature 343: 457-461: 1990
8) Wands JR, Fujita YK, Isselbacher KJ, et al: Identification and transmission of hepatitis B virus-related variants. Proc Natl Acad Sci USA 83: 6608-6612: 1986
9) Yamamoto K, Horikita M, Tsuda F, et al: Naturally occurring escape mutants of hepatitis B virus with various mutations in the S gene in carriers seropositive for antibody to hepatitis B surface antigen. J Virol 68: 2671-2676: 1994
10) Carman WF, van Deursen FJ, Mimms LT, et al: The prevalence of surface antigen variants of hepatitis B virus in Papua New guinea, South Africa and Sardinia. Hepatology 26: 1658-1666: 1997
11) 8. Chaudhuri V, Tayal R, Nayak B, et al: Occult hepatitis B virus infection in chronic liver disease: full-length genome and analysis of mutant surface promoter. Gastroenterology 127: 1356-1371: 2004
12) Hass M, Hannoun C, Kalinina T, et al: Functional analysis of hepatitis B virus reactivating in hepatitis B surface antigen-negative individuals. Hepatology 42: 93-103: 2005
13) Blum HE, Galun E, Liang TJ, et al: Naturally occurring missense mutation in the polymerase gene terminating hepatitis B virus replication. J Virol 65: 1836-1842: 1991
14) Okamoto H, Yotsumoto S, Akahane Y, et al: Hepatitis B viruses with precore region defects prevail in persistently infected hosts along with seroconversion to the antibody against e antigen. J Virol 64: 1298-1303: 1990
15) Akahane Y, Yamanaka T, Suzuki H, et al: Chronic active hepatitis with hepatitis B virus DNA and antibody against e antigen in the serum. Disturbed synthesis and secretion of e antigen from hepatocytes due to a point mutation in the precore region. Gastroenterology 99: 1113-1119: 1990
16) Kosaka Y, Takase K, Kojima M, et al: Fulminant

hepatitis B: induction by hepatitis B virus mutants defective in the precore region and incapable of encoding e antigen. Gastroenterology 100: 1087–1094: 1991
17) Omata M, Ehata T, Yokosuka O, et al: Mutations in the precore region of hepatitis B virus DNA in patients with fulminant and severe hepatitis. N Engl J Med 324: 1699–1704: 1991
18) Okamoto H, Tsuda F, Akahane Y, et al: Hepatitis B virus with mutations in the core promoter for an e antigen-negative phenotype in carriers with antibody to e antigen. J Virol 68: 8102–8110: 1994
19) Sato S, Suzuki K, Akahane Y, et al: Hepatitis B virus strains with mutations in the core promoter in patients with fulminant hepatitis. Ann Intern Med 122: 241–248: 1995
20) Parekh S, Zoulim F, Ahn SH, et al: Genome replication, virion secretion, and e antigen expression of naturally occurring hepatitis B virus core promoter mutants. J Virol 77: 6601–6612: 2003
21) Orito E, Mizokami M, Sakugawa H, et al: A case-control study for clinical and molecular biological differences between hepatitis B viruses of genotypes B and C. Japan HBV Genotype Research Group. Hepatology 33: 218–223: 2001
22) Yotsuyanagi H, Hino K, Tomita E, et al: Precore and core promoter mutations, hepatitis B virus DNA levels and progressive liver injury in chronic hepatitis B. J Hepatol 37: 355–363: 2002
23) Kanai K, Kako M, Aikawa T, et al: Core promoter mutations of hepatitis B virus for the response to interferon in e antigen-positive chronic hepatitis B. Am J Gastroenterol 91: 2150–2156: 1996
24) Erhardt A, Reineke U, Blondin D, et al: Mutations of the core promoter and response to interferon treatment in chronic replicative hepatitis B. Hepatology 31: 716–725: 2000
25) Baptista M, Kramvis A, Kew MC: High prevalence of 1762(T) 1764(A) mutations in the basic core promoter of hepatitis B virus isolated from black Africans with hepatocellular carcinoma compared with asymptomatic carriers. Hepatology 29: 946–953: 1999
26) Takahashi K, Akahane Y, Hino K, et al: Hepatitis B virus genomic sequence in the circulation of hepatocellular carcinoma patients: comparative analysis of 40 full-length isolates. Arch Virol 143: 2313–2326: 1998
27) Tanaka Y, Mukaide M, Orito E, et al: Specific mutations in enhancer II/core promoter of hepatitis B virus subgenotypes C1/C2 increase the risk of hepatocellular carcinoma. J Hepatol 45: 646–653: 2006
28) Ehata T, Omata M, Yokosuka O, et al: Variations in codons 84-101 in the core nucleotide sequence correlate with hepatocellular injury in chronic hepatitis B virus infection. J Clin Invest 89: 332–338: 1992
29) Fujiwara K, Yokosuka O, Ehata T, et al: The two different states of hepatitis B virus DNA in asymptomatic carriers: HBe-antigen-positive versus anti-HBe-positive asymptomatic carriers. Dig Dis Sci 43: 368–376: 1998
30) Lok AS, Lai CL, Leung N, et al: Long-term safety of lamivudine treatment in patients with chronic hepatitis B. Gastroenterology 125: 1714–1722: 2003
31) Akuta N, Suzuki F, Suzuki Y, et al: Favorable efficacy of long-term lamivudine therapy in patients with chronic hepatitis B: an 8-year follow-up study. J Med Virol 75: 491–498: 2005
32) Yatsuji H, Noguchi C, Hiraga N, et al: Emergence of a novel lamivudine-resistant hepatitis B virus variant with a substitution outside the YMDD motif. Antimicrob Agents Chemother 50: 3867–3874: 2006
33) Shaw T, Locarnini S: Entecavir for the treatment of chronic hepatitis B. Expert Rev Anti Infect Ther 2: 853–871: 2004
34) Lee YS, Suh DJ, Lim YS, et al: Increased risk of adefovir resistance in patients with lamivudine-resistant chronic hepatitis B after 48 weeks of adefovir dipivoxil monotherapy. Hepatology 43: 1385–1391: 2006
35) Schildgen O, Sirma H, Funk A, et al: Variant of hepatitis B virus with primary resistance to adefovir. N Engl J Med 354: 1807–1812: 2006
36) Lampertico P, Viganò M, Manenti E, et al: Low resistance to adefovir combined with lamivudine: a 3-year study of 145 lamivudine-resistant hepatitis B patients. Gastroenterology 133: 1445–1451: 2007
37) Gish RG, Lok AS, Chang TT, et al: Entecavir therapy for up to 96 weeks in patients with HBeAg-positive chronic hepatitis B. Gastroenterology 133: 1437–1444: 2007
38) Sherman M, Yurdaydin C, Sollano J, et al: Entecavir for treatment of lamivudine-refractory, HBeAg-positive chronic hepatitis B. Gastroenterology 130: 2039–2049: 2006
39) Tenney DJ, Levine SM, Rose RE, et al: Clinical emergence of entecavir-resistant hepatitis B virus requires additional substitutions in virus already resistant to Lamivudine. Antimicrob

Agents Chemother 48 : 3498-3507 : 2004
40) 鈴木文孝，鈴木義之，芥田憲夫，他：Lamivudine 耐性ウイルスに対して Entecavir を投与した B 型慢性肝炎例から検出された新たな Entecavir 耐性ウイルス，肝臓 46 ; 523 : 2005

論文受領，平成19年12月26日
受理，平成20年1月7日

International Journal of
HEMATOLOGY

Review Article

Intravenous Immunoglobulin Therapy for Acquired Coagulation Inhibitors: A Critical Review

Koji Yamamoto,[a] Junki Takamatsu,[a] Hidehiko Saito[b]

[a]*Department of Transfusion Medicine, Nagoya University Hospital, Nagoya, Japan;*
[b]*Nagoya Central Hospital, Nagoya, Japan*

Received November 27, 2006; received in revised form January 23, 2007; accepted February 6, 2007

Abstract

Intravenous immunoglobulin (IVIG) therapy has been used for autoimmune diseases and disorders involving autoantibodies, including coagulation inhibitors. In this review, we have evaluated the efficacy and safety of IVIG therapy for acquired coagulation inhibitors, including factor VIII inhibitor, and for acquired von Willebrand syndrome on the basis of 44 reports published between 1965 and 2005. Among 35 patients with factor VIII inhibitor, we estimated the efficacy of IVIG therapy alone (which includes complete remissions and partial responses with a clinical benefit) to be 30% (11 cases), whereas the response to combination therapy with IVIG plus immunosuppressive agents (eg, corticosteroid, cyclophosphamide) seemed to be better (approximately 70%, 33/45 cases) than with IVIG therapy alone. In acquired von Willebrand syndrome, the efficacy of IVIG therapy was estimated to be 30%. The response to IVIG therapy appears to occur rapidly, and coagulation inhibitors seem to be neutralized immediately. Moreover, severe complications or side effects rarely occur during IVIG treatment. IVIG therapy thus may be considered one choice for treating acquired coagulation inhibitors, although its efficacy improves when used in combination with immunosuppressive agents.
Int J Hematol. 2007;85:287-293. doi: 10.1532/IJH97.06222

Key words: Intravenous immunoglobulin therapy; Acquired coagulation inhibitors; Autoimmune disease; Factor VIII inhibitor; von Willebrand syndrome

1. Introduction

Intravenous immunoglobulin (IVIG), a highly purified immunoglobulin G (IgG) fraction derived from pooled human plasma, is currently one of the most widely used plasma components in the world [1,2]. It was originally introduced as replacement therapy for patients with primary immunodeficiency disorders. In 1981, Imbach et al reported a serendipitous observation that a high-dose infusion of IVIG (2 g/kg of body weight infused over 5 days) was able to transiently increase the platelet count in children with idiopathic thrombocytopenic purpura (ITP) [3]. With the encouragement of this and other reports on ITP [4], the clinical applications of IVIG have increased markedly over the past 25 years to include many autoimmune diseases. IVIG has been shown to be efficacious in clinical trials for graft-versus-host disease [5], myasthenia gravis [6], Guillain-Barré syndrome [7], Kawasaki disease [8], and chronic inflammatory demyelinating polyneuropathy [9]. It has also been used to treat immune neutropenia and coagulation inhibitors [10-12], but its efficacy and safety have not been firmly established.

Coagulation inhibitors, antibodies against individual clotting factors, interfere with blood coagulation. The most common coagulation inhibitor is factor VIII inhibitor, an antibody against factor VIII that neutralizes the coagulant activity of factor VIII. Factor VIII inhibitor develops in patients with hemophilia A as an alloantibody after replacement therapy or spontaneously as an autoantibody in nonhemophilic patients [13], including postpartum patients and those with autoimmune disease, malignancy, or diabetes [14]. Once developed in such patients, factor VIII inhibitor poses a serious problem for the management of bleeding episodes, because any infused factor VIII will be rapidly neutralized and will not be available to induce hemostasis [15]. Although IVIG therapy has been used as one of the immunotherapies

Correspondence and reprint requests: Koji Yamamoto, Department of Transfusion Medicine, Nagoya University Hospital, Nagoya, Japan; fax: 81-052-744-2610 (e-mail: kojiy@med.nagoya-u.ac.jp).

for eradicating coagulation inhibitors, such an indication is considered off label [2].

The aim of this review is to examine the efficacy and safety of IVIG therapy in patients with acquired inhibitors against factors VIII, IX, or V, and in patients with acquired von Willebrand disease. Cases with lupus anticoagulant were not included in this review. An electronic search of the Medline/PubMed database from 1965 to 2005 was performed to identify relevant articles. This search yielded 108 citations, 72 of which were considered appropriate and reviewed. The bibliography of each review paper was examined to identify articles that may have been missed by our electronic searches.

2. History

In 1983, Nilsson et al reported an interesting observation [11]. A patient with severe hemophilia B and factor IX inhibitor was treated with extracorporeal protein A–Sepharose adsorption to remove the inhibitor, followed by the administration of factor IX concentrate and cyclophosphamide. This procedure produced a 15-fold increase in factor IX inhibitor on one occasion but did not cause any increase of the inhibitor titer on another occasion, when 5 g of IVIG was also given to the patient to restore the reduced IgG level. The investigators suggested that the administration of IVIG appeared to suppress antibody synthesis in hemophilia B patients with factor IX inhibitor.

Three groups of investigators reported the use of IVIG in the management of factor VIII inhibitors in 1984 [12,16,17]. IVIG therapy combined with vincristine produced a transient disappearance of acquired factor VIII inhibitor along with a slow rise of factor VIII activity in a 13-year-old boy with autoimmune disease [16]. IVIG therapy was ineffective in 2 patients with hemophilia A inhibitor [17]. Sultan et al [12] reported that IVIG therapy (0.4 g/kg body weight per day for 5 days) resulted in the rapid, marked, and prolonged suppression of factor VIII inhibitor in 2 patients with acquired factor VIII antibody (autoantibody) but that it had little or no effect in 2 hemophilic patients with factor VIII antibody (alloantibody). They showed by in vitro experiments that IVIG preparations were able to neutralize the anti–factor VIII activity of the patients' plasma and the IgG fraction of the patients' sera. Many articles were subsequently published on the effect of IVIG on acquired factor VIII inhibitors, as is discussed later.

3. Possible Mechanisms of Action

The rapid rise in the platelet count in ITP following IVIG administration is thought to occur through binding to and blocking Fcγ receptors on macrophages, thereby preventing the removal of antibody-coated platelets by the reticuloendothelial system in the spleen and liver [4]. This mechanism, however, does not appear to explain the effect on coagulation inhibitors.

Several hypotheses on the mechanisms of action of IVIG on factor VIII inhibitor have been put forward. Sultan et al and Kazatchkine and Kaveri postulated that anti-idiotypic antibodies present in IVIG preparations neutralize factor VIII autoantibodies [12,18]. $F(ab')_2$ fragments from IVIG preparations inhibited anti–factor VIII activity in $F(ab')_2$ fragments from the patient's plasma. Anti–factor VIII $F(ab')_2$ fragments were specifically retained on an affinity column of Sepharose-bound $F(ab')_2$ from IVIG, indicating that a direct interaction occurred through the antibody-binding sites of both immunoglobulins [19]. Anti-idiotypes against various autoantibodies were shown to be present in pooled normal human polyspecific immunoglobulin. In addition, IgG prepared from elderly donors and multiparous women was reported to contain a higher frequency of neutralizing antibodies against factor VIII autoantibodies [20]. It is puzzling that such an in vitro antibody-neutralizing effect was not always demonstrated, even though in vivo administration of IVIG produced a marked reduction of the inhibitor titer [21,22].

The fall in inhibitor titer following IVIG therapy without simultaneous immunosuppressive treatment appears to be rapid (within several days) in most cases [12,23,24] but is slow (more than 10 days) in others [22,25]. There must be slow effects of IVIG on autoantibody production. In addition to its direct and immediate action on antibodies, IVIG has been proposed to suppress antibody formation by B-cells, a process mediated through the down-regulation of Fcγ receptors [26]. Furthermore, IVIG may induce T-cell suppressor activity [27]. These observations taken together suggest that IVIG exerts its effect on the inhibitor titer through more than one mode of action.

4. Efficacy

4.1. Factor VIII Inhibitor

We extensively reviewed the international literature published from 1965 to 2005. The typical IVIG dosage used for treating factor VIII inhibitor was 0.4 g/kg per day for 5 consecutive days.

The efficacy criteria (ie, the response to IVIG therapy) were as follows [28]: Complete remission (CR) was defined as the disappearance of the inhibitor, partial response (PR) was defined as a decrease in the inhibitor titer by at least 25% of the baseline value, and failure was defined as other than CR and PR.

In Table 1, we present all of the cases in which the efficacy of IVIG treatment alone was evaluated [12,22-25,28-40]. The response to IVIG therapy alone was failure in 11 cases (31.4%) and PR in 21 cases (60.0%), but with a subsequent clinical benefit in only 8 patients. Finally, 3 patients (8.6%) achieved CR. The efficacy of IVIG therapy alone, which includes CR and PR with a clinical benefit, among these 35 patients was estimated to be 31.4% (11 cases). In most cases of CR or PR, the response to IVIG treatment was rapid, and factor VIII inhibitor seemed to be neutralized immediately.

We summarize the responses to combined therapy with IVIG plus immunosuppressive agents in Table 2 [21,25, 28,32,35,38-52]. The response to IVIG plus steroid and/or cyclophosphamide therapy was better than to IVIG treatment alone. CR was achieved in 19 (73%) of 26 patients who were treated with IVIG plus steroid. In addition, 14 (74%) of 19 patients who received IVIG plus steroid and

Table 1.
Evaluable Patients from the Literature with Acquired Factor VIII Inhibitor Who Were Treated with Intravenous Immunoglobulin (IVIG)*

No.	Reference	Sex/Age, y	Associated Disease	IVIG Dosage, g/kg per d	Inhibitor Titer, Bethesda U		Response	Clinical Outcome
					Before	Nadir (d†)		
1	Hudak et al [29]	F/40	Postpartum	0.5 × 5 d	16	<1 (105)	CR	Sustained remission
2	Schwartz et al [25]	M/68	CLL	1 × 2 d	1	0 (14)	CR	Sustained remission
3	Schwartz et al [25]	F/83	Diabetes	1 × 2 d	0.9	0 (61)	CR	Sustained remission
4	Sultan et al [12]	M/62	Idiopathic	0.4 × 5 d	25,000	550 (3)	PR	No clinical benefit‡
5	Sultan et al [12]	F/29	Postpartum	0.4 × 5 d	10,500	1000 (3)	PR	No clinical benefit
6	Zimmermann et al [30]	F/64	Idiopathic	0.5 × 8 d	75	10 (25)	PR	Clinical benefit
7	Zimmermann et al [30]	F/70	Idiopathic	0.5 × 8 d	51	3.8 (9)	PR	Clinical benefit
8	Newland et al [22]	F/71	Diabetes	0.4 × 5 d	50	20 (45)	PR	Clinical benefit
9	Heyman et al [31]	M/64	Idiopathic	0.4 × 5 d	47	28 (17)	PR	No clinical benefit
10	Nishida et al [23]	F/39	Idiopathic	0.4 × 5d	115	17 (3)	PR	No clinical benefit
11	Schwerdtfeger et al [32]	F/31	Postpartum	0.5 × 5 d	420	104 (6)	PR	No clinical benefit
12	Sultan et al [33]	M/78	NA	0.4 × 5 d	42	20 (30)	PR	No clinical benefit
13	Sultan et al [33]	M/72	Carcinoma	0.4 × 5 d	38	10 (5)	PR	Transient benefit
14	Schwartz et al [25]	M/54	Alcoholism	1 × 2 d	1228	208 (7)	PR	No clinical benefit
15	Schwartz et al [25]	F/72	Idiopathic	1 × 2 d	880	570 (48)	PR	No clinical benefit
16	Schwartz et al [25]	F/25	Idiopathic	1 × 2 d	280	1.9 (57)	PR	Clinical benefit
17	Schwartz et al [25]	F/38	Postpartum	1 × 2 d	102	56 (22)	PR	Clinical benefit
18	Schwartz et al [25]	M/77	Carcinoma	0.4 × 5 d	39	24 (3)	PR	No clinical benefit
19	Schwartz et al [25]	M/60	Griseofulvin	0.4 × 5 d	29	18 (19)	PR	No clinical benefit
20	Crenier et al [28]	M/65	Cardiomyopathy	0.4 × 5 d	120	72 (30)	PR	No clinical benefit
21	Crenier et al [28]	M/74	Bronchitis	0.4 × 5 d	24	12 (7)	PR	No clinical benefit
22	Michiels et al [24]	F/31	Postpartum	0.5 × 5 d	12	1 (11)	PR	Clinical benefit
23	Lafferty et al [34]	F/42	SLE	0.4 × 5 d	500	185 (NA)	PR	Clinical benefit
24	Walsh et al [35]	F/72	Cholecystitis	30 g × 1 d	6	NA	PR	Clinical benefit
25	Hiller et al [36]	M/57	Surgery	30 g × 5 d	24	20 (2)	F	Transient benefit
26	Casas et al [37]	M/70	Lymphoma	0.4 × 7 d	8.6	35 (NA)	F	Transient benefit
27	Sultan et al [33]	M/45	Vasculitis	0.4 × 5 d	25	28 (NA)	F	NA
28	Pignone et al [38]	F/66	RA	0.4 × 6 d	13	26 (7)	F	NA
29	Hauser et al [39]	F/29	Postpartum	0.4 × 5 d	10	110 (NA)	F	NA
30	Mateo et al [40]	F/82	CLL	0.4 × 5 d	9.5	10 (30)	F	NA
31	Schwartz et al [25]	M/64	Diabetes	1 × 2 d	452	340 (6)	F	No clinical benefit
32	Schwartz et al [25]	F/83	LA	0.4 × 5 d	102	96 (5)	F	No clinical benefit
33	Schwartz et al [25]	F/48	Idiopathic	1 × 2 d	59	46 (2)	F	No clinical benefit
34	Schwartz et al [25]	M/73	Carcinoma	0.4 × 5 d	42	108 (5)	F	No clinical benefit
35	Schwartz et al [25]	M/62	Idiopathic	1 × 2 d	1.4	1.4 (11)	F	No clinical benefit

*CR indicates complete remission; CLL, chronic lymphocytic leukemia; PR, partial response; NA, not available; SLE, systemic lupus erythematosus; F, treatment failure; RA, rheumatoid arthritis; LA, lupus anticoagulant.

†Number of days after starting IVIG treatment.

‡Subjective evaluation by the doctors in charge.

cyclophosphamide reached CR. Only 2 cases of treatment with IVIG plus cyclophosphamide were reported, and these patients achieved CR [52]. Conversely, 18 (75%) of 24 patients treated with steroid plus cyclophosphamide instead of IVIG achieved CR. This degree of efficacy is consistent with the report by Green et al [45]. In these reports, however, the evaluation of efficacy depended on the patients' symptoms (ie, improvement of bleeding tendency), because the disappearance of inhibitors was not followed up.

Thus, the overall efficacy of IVIG therapy alone is almost 30%, whereas that of a combination therapy with IVIG plus steroid and/or cyclophosphamide is approximately 70%.

Recent reports have described patients with acquired factor VIII inhibitors who rapidly responded to immunosuppressive regimens including rituximab, a monoclonal antibody against CD20+ B-cells [53,54]. These data suggest that immunosuppressive therapy using rituximab could become a powerful tool against coagulation inhibitors.

4.2. Acquired von Willebrand Syndrome

Acquired von Willebrand syndrome is a rare bleeding disorder with laboratory findings similar to those of congenital von Willebrand disease. According to an international registry, acquired von Willebrand syndrome is primarily associated with lymphoproliferative diseases, immunologic and cardiovascular disorders, and solid tumors. The prevalence of acquired von Willebrand syndrome in these underlying disorders is still unknown.

IVIG was also effective in stopping bleeding in acquired von Willebrand syndrome [55]. Several groups reported that acquired von Willebrand syndrome associated with systemic lupus erythematosus [56], monoclonal gammopathy [57-60], malignant lymphoma [61], and prostatomegaly [62], and of undefined origin [63,64] responded well to IVIG therapy. Some patients were successfully treated with the combination of IVIG and desmopressin, but the effect was transient

Table 2.
Responses of Patients with Acquired Factor VIII Inhibitor to Immunosuppressive Agents with or without Intravenous Immunoglobulin (IVIG) Therapy

	IVIG + Pr (26 Cases)			IVIG + Pr + Cy (19 Cases)			Pr + Cy (24 cases)		
Reference	CR	PR	F	CR	PR	F	CR	PR	F
Green et al [41]	1								
Carreras et al [21]	1								
Heyman et al [31]			1†						
OiSullivan et al [42]					1				
Pirner et al [43]					1				
Lionett et al [44]	1								
Pignone et al [38]							1		
Green et al [45]							5		5
Hauser et al [39]							1		
Mateo et al [40]	1								
Schwartz et al [25]	1	1							
Crenier et al [28]	1			1					
Lafferty et al [34]					1				
Sohngen et al [46]							2		
Bossi et al [47]	4		1	8		1	3		
Gandini et al [48]	1								
Dykes et al [49]	4	1	2						
Grunewald et al [50]				2			4		
Mazzucconi et al [51]	3	1							
Delgado et al [52]	1			3	1		2		1
Total	19	3	4	14	4	1	18		6

*Pr indicates prednisolone or dexamethasone; Cy, cyclophosphamide; CR, complete remission; PR, partial response; F, treatment failure.
†IVIG dosage: 0.4 g/kg per d for 2 d.

in most cases. According to data from an international registry, the efficacy of IVIG therapy in acquired von Willebrand syndrome was estimated to be 30% (21/63 patients) [65,66]. Of note, however, is that in most cases the efficacy of IVIG was subjectively evaluated (ie, a good response means to stop bleeding) by the doctors in charge. This efficacy is similar to that for treatment with desmopressin (38/119) or with immunosuppressive agents (23/66), but corticosteroids alone were effective in only 19% of patients (12/63).

4.3. Other Coagulation Inhibitors (Factor V or IX Inhibitor)

Patients with inhibitors against factor V or IX are extremely rare. Only one report described acquired factor IX inhibitor developing in a patient with autoimmune polymyositis [67]. Single-agent therapy with IVIG was effective in suppressing inhibitor synthesis and in stopping bleeding. Another report described acquired factor V inhibitor developing in an 82-year-old female patient following abdominal surgery [68]. Nine-day treatment with IVIG (0.4 g/kg per day) was partially effective in suppressing the inhibitor titer and improving the patient's hemorrhagic diathesis.

5. Safety

Adverse reactions to IVIG therapy are usually mild and self-limited: headache, back pain, low-grade fever, myalgia, and chills. The IVIG preparations currently in clinical use are also assumed to carry virtually no risk of transmitting infectious agents. Rarely, however, serious complications can occur. In recent years, thromboembolic complications have occasionally been reported in patients who received IVIG. Stroke, acute myocardial infarction, and deep vein thrombosis were estimated to occur at an incidence of 3% to 5% [69]. Thromboembolism appeared to develop mainly in patients who had other risk factors, such as an advanced age, being bedridden, and a history of thromboembolism. What triggers thromboembolic complications? During 5 courses of treatment with IVIG (24-54 g/day), the plasma IgG concentration was noted to increase 4-fold, and plasma viscosity increased to beyond the normal range [70]. It appears that increased blood viscosity after high-dose IVIG infusion is responsible for thromboembolism. Slow infusion of IVIG (a daily dose of 0.4 g/kg in not less than 8 hours) has been recommended to prevent thromboembolism [71].

Interestingly, our own review of the literature revealed no thromboembolic complications in 80 patients with acquired factor VIII inhibitor who had received IVIG. It is tempting to speculate that the presence of a coagulation inhibitor may counteract thrombosis formation.

6. Discussion

In general, treatments of acquired coagulation inhibitors are divided into 2 approaches: One is to stop the present bleeding events, and the other is to remove inhibitors by immunomodulative therapy. In cases of acute bleeding in patients with factor VIII inhibitors, conventional management consists of human factor VIII concentrate or desmopressin for low inhibitor levels (<5 Bethesda U) and porcine factor VIII or bypass therapy (eg, recombinant activated

factor VII, activated prothrombin complex concentrates) for high inhibitor levels (>5 Besthesda U). On the other hand, immunosuppressive agents (eg, corticosteroid, cyclophosphamide, azathioprine, rituximab) or IVIG has been used to suppress the generation of coagulation inhibitors. Other approaches are plasmapheresis and immunoadsorption using a protein A–Sepharose column to remove coagulation inhibitors, but the indications for these therapies are limited.

Evaluation of the response to one therapeutic modality in the management of coagulation inhibitors is not always easy, for a number of reasons. First, there are only a few inhibitor patients, and thus it is almost impossible to conduct a randomized clinical trial. There have been only a few such trials on acquired coagulation inhibitors [25,45]. This situation influences the evaluation of efficacy because cases of unsuccessful treatment with IVIG may not have been reported, with only successful cases having been evaluated. Second, most patients present with life-threatening bleeding and are treated with several different therapies simultaneously or sequentially. It is difficult, therefore, to assess the outcome of any single modality. Third, it is known that spontaneous fluctuation or disappearance of the inhibitor may occur [72].

As is shown in Table 1, the efficacy of IVIG therapy alone is not very high (ie, 30%). Moreover, the CR rates for combination therapy with IVIG plus glucocorticoid and/or cyclophosphamide (IVIG plus prednisolone/dexamethasone, 73%; IVIG plus prednisolone/dexamethasone and cyclophosphamide, 74%) did not differ from those of immunosuppressive agents without IVIG (prednisolone/dexamethasone plus cyclophosphamide, 75%) (Table 2). However, the clinical benefits of IVIG include a rapid response and fewer adverse effects, which are frequently observed with the chronic administration of glucocorticoid or other immunosuppressive agents. Regarding the use of cyclophosphamide in particular, it is possible for cytotoxicity to induce myelosuppression and secondary malignancy. Thus, IVIG therapy should be considered for acute massive bleeding in patients with acquired coagulation inhibitors because of its faster action. On the other hand, IVIG therapy costs approximately US $10,000 for a 5-day infusion, which is much more costly than other treatments except rituximab. These considerations taken together suggest that the use of IVIG for the management of acquired coagulation inhibitors might be limited, because whether a given treatment is used depends on the balance between cost and benefit.

7. Conclusion

For patients with acquired coagulation inhibitors against factor VIII, the efficacy of IVIG therapy alone was estimated to be 30% in 35 cases. On the other hand, the response to combination therapy with IVIG plus immunosuppressive agents (eg, corticosteroid, cyclophosphamide) seems to be better (ie, 70% in 45 cases) than IVIG as single-agent therapy. IVIG may be considered as one choice of treatment for acquired coagulation inhibitors, especially when a rapid response is required without myelosuppression, but its use alone would be limited because of its lower efficacy and high cost.

References

1. NIH Consensus Conference. Intravenous immunoglobulin: prevention and treatment of disease. *JAMA*. 1990;264:3189-3193.
2. Knezevic-Maramica I, Kruskall MS. Intravenous immune globulins: an update for clinicians. *Transfusion*. 2003;43:1460-1480.
3. Imbach P, Barandun S, d'Apuzzo V, et al. High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. *Lancet*. 1981;1:1228-1231.
4. Fehr J, Hofmann V, Kappeler U. Transient reversal of thrombocytopenia in idiopathic thrombocytopenic purpura by high-dose intravenous gamma globulin. *N Engl J Med*. 1982;306:1254-1258.
5. Sullivan KM, Kopecky KJ, Jocom J, et al. Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation. *N Engl J Med*. 1990;323:705-712.
6. Gajdos P, Chevret S, Clair B, Tranchant C, Chastang C. Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. *Ann Neurol*. 1997;41:789-796.
7. van der Meche FGA, Schmitz PIM, for the Dutch Guillain-Barré Study Group. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. *N Engl J Med*. 1992;326:1123-1129.
8. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med*. 1986;315:341-347.
9. Hahn AF, Bolton CF, Zochodne D, Feasby TE. Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy: a double-blind, placebo-controlled, cross-over study. *Brain*. 1996;119:1067-1077.
10. Pollack S, Cunningham-Rundles C, Smithwick EM, Barandun S, Good RA. High dose intravenous gamma globulin for autoimmune neutropenia. *N Engl J Med*. 1982;307:253.
11. Nilsson IM, Sundqvist SB, Ljung R, Holmberg L, Freiburghaus C, Bjorlin G. Suppression of secondary antibody response by intravenous immunoglobulin in a patient with haemophilia B and antibodies. *Scand J Haematol*. 1983;30:458-464.
12. Sultan Y, Kazatchkine MD, Maisonneuve P, Nydegger UE. Anti-idiotypic suppression of autoantibodies to factor VIII (anti-haemophilic factor) by high-dose intravenous gammaglobulin. *Lancet*. 1984;2:765-768.
13. Green D, Lechner K. A survey of 215 non-hemophilic patients with inhibitors to factor VIII. *Thromb Haemost*. 1981;45:200-203.
14. Hauser I, Schneider B, Lechner K. Post-partum factor VIII inhibitors: a review of the literature with special reference to the value of steroid and immunosuppressive treatment. *Thromb Haemost*. 1995;73:1-5.
15. Hay CR, Colvin BT, Ludlam CA, Hill FG, Preston FE. Recommendations for the treatment of factor VIII inhibitors: from the UK Haemophilia Centre Directors' Organisation Inhibitor Working Party. *Blood Coagul Fibrinolysis*. 1996;7:134-138.
16. Gianella-Borradori A, Hirt A, Luthy A, Wagner HP, Imbach P. Haemophilia due to factor VIII inhibitors in a patient suffering from an autoimmune disease: treatment with intravenous immunoglobulin. A case report. *Blut*. 1984;48:403-407.
17. Seifried E, Gaedicke G, Pindur G, Rasche H. The treatment of haemophilia A inhibitor with high dose intravenous immunoglobulin. *Blut*. 1984;48:397-401.
18. Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. *N Engl J Med*. 2001;345:747-755.
19. Rossi F, Sultan Y, Kazatchkine MD. Anti-idiotypes against autoantibodies and alloantibodies to VIII:C (anti-haemophilic factor) are present in therapeutic polyspecific normal immunoglobulins. *Clin Exp Immunol*. 1988;74:311-316.
20. Dietrich G, Algiman M, Sultan Y, Nydegger UE, Kazatchkine MD. Origin of anti-idiotypic activity against anti-factor VIII autoantibodies in pools of normal human immunoglobulin G (IVIg). *Blood*. 1992;79:2946-2951.

21. Carreras LO, Perez GN, Xavier DL, Blanco AN, Penalva LB. Autoimmune factor VIII inhibitor responsive to gammaglobulin without in vitro neutralization. *Thromb Haemost*. 1988;60:343.
22. Newland AC, Macey MG, Moffat EH, Ainsworth M, Colvin BT. Effect of intravenous immunoglobulin on a spontaneous inhibitor to factor VIII. *Clin Lab Haematol*. 1988;10:435-442.
23. Nishida Y, Sakiyama N, Kakishita E, Nagai K. Evidence of the direct interaction between spontaneously occurring anti-factor VIII autoantibody and intravenous immunoglobulin. *Nippon Ketsueki Gakkai Zasshi*. 1989;52:134-139.
24. Michiels JJ, Hamulyak K, Nieuwenhuis HK, Novakova I, van Vliet HH. Acquired haemophilia A in women postpartum: management of bleeding episodes and natural history of the factor VIII inhibitor. *Eur J Haematol*. 1997;59:105-109.
25. Schwartz RS, Gabariel DA, Aledort LM, Green D, Kessler CM. A prospective study of treatment of acquired (auto-immune) factor VIII inhibitors with high-dose intravenous gammaglobulin. *Blood*. 1995;86:797-804.
26. Heyman B. Fc-dependent IgG-mediated suppression of the antibody response: fact or artifact? *Scand J Immunol*. 1990;31:601-607.
27. Dammacco F, Iodice G, Campobasso N. Treatment of adult patients with idiopathic thrombocytopenic purpura with intravenous immunoglobulin: effects in circulating T cell subsets and PWM-induced antibody synthesis in vitro. *Br J Haematol*. 1986;62: 125-135.
28. Crenier L, Ducobu J, des Grottes JM, Cerny J, Delaunoit C, Capel P. Low response to high-dose intravenous immunoglobulin in the treatment of acquired factor VIII inhibitor. *Br J Haematol*. 1996;95:750-753.
29. Hudak C, Spiridonidis CH, Hart AJ, Betras SA, Laufman LR. Pregnancy-associated factor VIII inhibitor: treatment with intravenous high-dose immunoglobulin. *Am J Hematol*. 1993;43:158.
30. Zimmermann R, Kommerell B, Harenberg J, Eich W, Rother K, Schimpf K. Intravenous IgG for patients with spontaneous inhibitor to factor VIII. *Lancet*. 1985;1:273-274.
31. Heyman MP, Chakravarthy A, Edelman BB, Needleman SW, Schiffer CA. Failure of high-dose i.v. gammaglobulin in the treatment of spontaneous acquired factor VIII inhibitors. *Am J Hematol*. 1988;28:191-194.
32. Schwerdtfeger R, Hintz G, Huhn D. Successful treatment of a patient with postpartum factor VIII inhibitor with recombinant human interferon α2a. *Am J Hematol*. 1991;37:190-193.
33. Sultan Y, Kazatchine MD, Nydegger U, Rossi F, Dietrich G, Algiman M. Intravenous immunoglobulin in the treatment of spontaneously acquired factor VIII:C inhibitors. *Am J Med*. 1991; 91(suppl 5A):35S-39S.
34. Lafferty TE, Smith JB, Schuster SJ, DeHoratius RJ. Treatment of acquired factor VIII inhibitor using intravenous immunoglobulin in two patients with systemic lupus erythematosus. *Arthritis Rheum*. 1997;40:775-778.
35. Walsh JD, Landercasper J, Bottner WA, Boyd WC. Cholecystectomy and acquired factor VIII inhibitor coagulopathy. *Am Surg*. 2004;70:815-817.
36. Hiller E, Holler E, Geursen RG, Riess H. Successful treatment with high-dose intravenous immunoglobulin in a patient with spontaneous inhibitor to factor VIII. *Blut*. 1986;52:123-126.
37. Casas E, Garcia Puig J, Villar A, Gonzalez Sanz A, Miranda ME, Ortiz Vazquez J. Sindrome hemorragico asociado a un inhibidor del factor VIII:C en un patiente con linfoma. *Med Clin (Barc)*. 1989;93:23-25.
38. Pignone A, Matucci-Cerinic M, Morfini M, et al. Suppression of autoantibodies to factor VIII and correction of factor VIII deficiency with a combined steroid-cyclophosphamide-porcine factor VIII treatment in a patient with rheumatoid arthritis. *J Intern Med*. 1992;231:617-619.
39. Hauser I, Gisslinger H, Locker G, et al. Postpartum factor VIII inhibitors: report of two cases with special reference to the efficacy of various treatments. *Wien Klin Wochenschr*. 1993;105:355-358.
40. Mateo J, Martino R, Borrell M, Gari M, Casas F, Fontcuberta J. Acquired factor VIII inhibitor preceding chronic lymphocytic leukemia. *Ann Hematol*. 1993;67:309-311.
41. Green D, Kwaan HC. An acquired factor VIII inhibitor responsive to high-dose gamma globulin. *Thromb Haemost*. 1987;58:1005-1007.
42. O'Sullivan JL, Haedicke GJ, Bevivino J. Spontaneous postpartum factor VIII inhibitor development with bleeding into the face and neck. *Plast Reconstr Surg*. 1989;84:802-805.
43. Pirner K, Rosler W, Kalden JR, Manger B. Long-term remission after i.v. immunoglobulin treatment in acquired AHF hemophilia with SLE [in German]. *Z Rheumatol*. 1990;49:378-381.
44. Lionett F, Gouault-Heilmann M, Azoulay C, Lacorte JM, Schaeffer A. Auto-immune factor VIII:C inhibitor durably responsive to immunoglobulin: a new case. *Thromb Haemost*. 1990;64:488-489.
45. Green D, Rademaker AW, Briet E. A prospective, randomized trial of prednisone and cyclophosphamide in the treatment of patients with factor VIII autoantibodies. *Thromb Haemost*. 1993;70:753-757.
46. Sohngen D, Specker D, Bach D, et al. Acquired factor VIII inhibitors in non-hemophilic patients. *Ann Hematol*. 1997;74:89-93.
47. Bossi P, Cabane J, Ninet J, et al. Acquired hemophilia due to factor VIII inhibitors in 34 patients. *Am J Med*. 1998;105:400-408.
48. Gandini G, Franchini M, Manzato F, Lippi G, Aprili G. A combination of prednisone, high-dose intravenous immunoglobulin and desmopressin in the treatment of acquired hemophilia A with high-titer inhibitor. *Haematologica*. 1999;84:1054.
49. Dykes AC, Walker ID, Lowe GD, Tait RC. Combined prednisolone and intravenous immunoglobulin treatment for acquired factor VIII inhibitors: a 2-year review. *Haemophilia*. 2001;7:160-163.
50. Grunewald M, Beneke H, Guthner C, Germowitz A, Brommer A, Griesshammer M. Acquired hemophilia: experiences with a standardized approach. *Haemophilia*. 2001;7:164-169.
51. Mazzucconi MG, Bizzoni L, Giorgi A, et al. Postpartum inhibitor to factor VIII: treatment with high-dose immunoglobulin and dexamethasone. *Haemophilia*. 2001;7:422-427.
52. Delgado J, Villar A, Jimenez-Yuste V, Gago J, Quintana M, Hernandez-Navarro F. Acquired hemophilia: a single-center survey with emphasis on immunotherapy and treatment-related side-effects. *Eur J Haematol*. 2002;69:158-164.
53. Jy W, Gagliano-DeCesare T, Kett DH, et al. Life-threatening bleeding from refractory acquired FVIII inhibitor successfully treated with rituximab. *Acta Haematol*. 2003;109:206-208.
54. Wiestner A, Cho HJ, Asch AS, et al. Rituximab in the treatment of acquired factor VIII inhibitors. *Blood*. 2002;100:3426-3428.
55. Federici AB, Stabile F, Castaman G, Canciani MT, Mannucci PM. Treatment of acquired von Willebrand syndrome in patients with monoclonal gammopathy of uncertain significance: comparison of three different therapeutic approaches. *Blood*. 1998;92:2707-2711.
56. Viallard J-F, Pellegrin JL, Vergnes C, et al. Three cases of acquired von Willebrand disease associated with systemic lupus erythematosus. *Br J Haematol*. 1999;105:532-537.
57. Agarwal N, Klix MM, Burns CP. Successful management with intravenous immunoglobulins of acquired von Willebrand disease associated with monoclonal gammopathy of undetermined significance. *Ann Intern Med*. 2004;141:83-84.
58. Gross S, Traulie C, Capiod JC, et al. Efficacy of high-dose intravenous gammaglobulin in the management of acquired von Willebrand's disease during orthopaedic surgery. *Br J Haematol*. 1992; 82:170-171.
59. Delmer A, Horellou MH, Brechot JM, et al. Acquired von Willebrand disease: correction of hemostatic defect by high-dose intravenous immunoglobulins. *Am J Hematol*. 1992;40:151-152.
60. van Genderen PJJ, Terpstra W, Michiels JJ, Kapteijn L, van Vliet HHDM. High-dose intravenous immunoglobulin delays clearance of von Willebrand factor in acquired von Willebrand disease. *Thromb Haemost*. 1995;73:891-892.
61. van Genderen PJJ, Michiels JJ, Bakker JJ, van 't Veer MB. Effectiveness of high-dose intravenous gamma globulin therapy in acquired von Willebrand's disease. *Vox Sang*. 1994;67:14-17.
62. Sampson B, Anderson DR, Dugal M, Ing VW, Zayed E. Acquired type 2a von Willebrand's disease: response to immunoglobulin infusion. *Haemostasis*. 1997;27:286-289.
63. White LA, Chisholm M. Gastro-intestinal bleeding in acquired von Willebrand's disease: efficacy of high-dose immuno-globulin where substitution treatments failed. *Br J Haematol*. 1993;84:332-334.

64. Arkel YS, Lynch J, Kamiyama M. Treatment of acquired von Willebrand syndrome with intravenous immunoglobulin. *Thromb Haemost*. 1994;72:643-644.
65. Federici AB, Rand JH, Bucciarelli P, et al. Acquired von Willebrand syndrome: data from an international registry. *Thromb Haemost*. 2000;84:345-349.
66. Federici AB. Use of intravenous immunoglobulin in patients with acquired von Willebrand syndrome. *Hum Immunol*. 2005;66:422-430.
67. Suzuki K, Murata H, Akiike T, et al. A case report of polymyositis with acquired factor IX inhibitor [in Japanese]. *Kanto Ryumachi*. 1995;29:38-47.
68. Buclin T, Schmidt PM, Hauert J, Winkel L, Chapuis G, Bachmann F. Acquired factor V inhibitor treated with intravenous immunoglobulins [in French]. *Schweiz Med Wochenschr*. 1992;122: 1968-1970.
69. Stangel M, Hartung HP, Marx P, Gold R. Side effects of high-dose intravenous immunoglobulins. *Clin Neuropharmacol*. 1997;20: 385-393.
70. Reinhart WH, Berchtold P. Effect of high-dose intravenous immunoglobulin therapy on blood rheology. *Lancet*. 1992;339: 662-664.
71. Katz U, Shoenfeld Y. Review: intravenous immunoglobulin therapy and thromboembolic complications. *Lupus*. 2005;14:802-808.
72. Lottenberg R, Kentro TB, Kitchens CS. A natural history study of 16 patients with factor VIII inhibitors receiving little or no therapy. *Arch Intern Med*. 1987;147:1077-1081.