表1　小児科領域における適応外使用解決と治験促進のためのアクションプラン

1) 適応外使用解決と小児治験促進を学会のミッションのひとつとする
(ア) この問題を学術集会，小児科学会雑誌などで積極的かつ継続的に取り上げる
(イ) 治験・臨床試験を理解する小児科医の育成を図る
①若手医師の研修支援
②医薬品医療機器総合機構などへの小児科医師派遣の推進
(ウ) 治験実施を業績として認める（たとえば小児科専門医の研修単位として認める）方向での働きかけを行う
(エ) 各分科会に薬事委員会を設立し取り組みを強化し，厚生労働科学研究大西班での活動へ発展させる
①適応外使用解決についての取り組み内容は，各分科会から業績として提出いただき，取り組みの記録と経験の蓄積を図る
(オ) 製薬企業や行政からの小児医薬品開発に関する諮問をうけられるような専門委員会を学会内に作る
(カ) 本アクションプランに従い，必要に応じて関係機関へ要望書を提出する
2) 適応外使用医薬品の全体のカテゴリー分けをすすめ，それぞれについて解決の方策を探る
(ア) 抗がん剤併用療法の適応拡大スキームのごとく，国内外のエビデンス，あるいは市販後調査結果とエビデンスの総合判断等により，適応拡大や添付文書の改訂が可能な医薬品も数多くあるもの期待される
①規制当局との話し合いが必須
②カテゴリー分けの方法についての検討
③医薬品の選定，評価できる体制（人材も）の整備
④必要に応じて分科会同士，あるいは成人領域との連携
(イ) プライオリティリストの内容の吟味・更新と整理
①一部に評価の高い対応もみられるが，分科会によって対応がまちまちであり，全体的に質を上げたプライオリティリストの作成が望まれる
②各分科会において実働できる若手の育成が必須
③医師主導治験の必要な医薬品の厳選（場合によっては分科会同士，あるいは成人領域との話し合いが必要）
3) 試薬，各医療機関で化学合成あるいは剤型を変更して使用している薬品，もしくは個人輸入医薬品等の問題解決の枠組み作り
(ア) 実態把握を行い，解決の方策を探り，関係機関との話し合いをもつ
(イ) 製薬企業によって開発され，正式に承認されることが好ましい．そのためには，製薬企業へのインセンティブ，プロトコル作成支援，補助金制度のなどの体制作りについて，関係機関との話し合いが必要
(ウ) これまでの規制当局の対応の見直しを要請
①たとえば，海外で十分にエビデンスがある医薬品に対して，新規医薬品として非臨床試験を厳密に課すことがジアゾキサイドなどの承認の障害となっている．見直しを求めることが必要
4) 小児治験の体制整備
(ア) 大規模治験ネットワークを成功させる
①平成15年度に選考された治験薬のクエン酸フェンタニルは平成16年秋の治験開始を目標に準備中
②平成16年度の品目候補薬の絞り込みと，プロトコル案（少なくとも骨子）を作成する必要あり（各分科会での活動が重要）
③今後の予算獲得を円滑にするためにも，小児科領域の実績を上げる必要がある
(イ) 小児治験体制整備の支援への関係機関への働きかけ
①治験管理体制の立ち上げの援助のみでなく，人件費についての援助が必須
②小児治験・臨床試験を理解した人材の育成
(ウ) 小児臨床試験の体制整備にもつなげられるような枠組み作りが理想
5) 製薬企業へのインセンティブの立法化についての働きかけ
(ア) 特許権延長，薬価優遇，優遇税制など
(イ) 手続きの優先や，手続き量の減免
(ウ) 特許権切れ・再審査期間終了後の古い医薬品や，個人輸入薬，試薬などの開発のインセンティブや支援体制も必要

表1　つづき

（エ）小児医薬品の薬価設定基準の見直しの要請
①これまでも，小児科学会からの依頼を受けて開発された医薬品が価格面での折り合いがつかずに市場に上らなかったことがある．こうした事態は小児医薬品開発の抑制につながることになる
6）小児治験の要請権，義務化についての働きかけ
（ア）立法化への働きかけが必要
①たとえば，厚生労働省に小児治験の要請権
（イ）小児医薬品開発の諮問委員会，必要であれば規制当局に担当部署の設置
①委員会の質の維持が重要
②小児科医を規制当局に派遣し，薬事行政を理解した小児科医を増やすことが必要
③小児臨床試験のトレーニングを受けた小児科医が必要
7）市販後調査・使用実態調査を活用した小児の情報収集の枠組み作り
（ア）学会として製薬企業の市販後調査に協力（例：タミフルの1歳未満の特別調査）
（イ）公的な研究費による使用実態調査：医薬品医療機器総合機構などとの連携ができないか
（ウ）添付文書（使用上の注意や安全性としての情報など）に反映させることを目標
8）妊娠および授乳中の医薬品投与の安全性情報充実に向けての活動
（ア）関連学会，関連機関との連携が必要
（イ）海外での取り組みなどを参考に，日本における取り組みについての検討を行う
（ウ）情報収集し，添付文書に反映させることを目標

表2　カテゴリー分類

1）海外で承認されている，あるいは海外で治験中であるが，まだ国内に製剤がない（原則として新規性の高い）医薬品
2）海外で承認されている臨床上不可欠な比較的古い医薬品で，国内に製剤がないもの
3）試薬を転用している医薬品，施設で化学合成している医薬品など
4）国内に同一有効成分の医薬品はあるが，必要な剤型がないもの（例：現在，脱カプセル，錠剤つぶし，静注用製剤の経口投与で対応している場合等）
5）国内に同一有効成分及び同一剤型の医薬品はあるが，小児（あるいは特定の年齢群）の必要な適応（以下「新規適応」という）がないもの
（ア）小児（あるいは特定の年齢群）の他の適応はある（用量や安全性の評価がある程度されている）
①成人や他年齢群でも新規適応がない
②成人や他年齢群では新規適応がある
（イ）小児（あるいは特定の年齢群）の他の適応もない
③成人や他年齢群でも新規適応がない
④成人や他年齢群では新規適応がある
6）国内に同一有効成分，同一剤型及び同一適応の医薬品はあるが，小児（あるいは特定の年齢群）の用量が不明確のもの
（ウ）海外（米，英，独，仏など，承認審査に係る薬事規制が我が国と同等と考えられる国．以下同じ．）の添付文書でも明確な記載がない
（エ）海外の添付文書では明確な記載がある
7）小児での安全性が確立していないもの，安全性の記載が不十分あるいは行過ぎているもので，保険で査定される可能性が比較的高い等の問題があるもの

表3　対象医薬品の優先度決定の基準

以下の（ア）に記載されているレベルのエビデンスがあり，かつ，（イ）のいずれかを満たす医薬品について，（ウ）の観点も加味して優先度を決定する．

（ア）エビデンスレベル

①アメリカ，イギリス，ドイツ及びフランスなど承認審査に係る薬事規制が我が国と同等と考えられる国で承認された効能・効果及び用法・用量をもつ医薬品が原則

②①でない場合，複数の第III相試験がある，あるいは多くの世界的に認められた教科書に標準的治療として記載されている等，エビデンスが十分にあると考えられる医薬品

（イ）適応疾病の重篤度等

①適応疾病が重篤であり，生命に重大な影響がある疾患

②適応疾病が重篤であり，病気の進行が不可逆及び/または日常生活に著しい影響を及ぼす疾患

③その他（例：適応疾病は重篤でないが日常生活に著しい影響を及ぼす疾患）

（ウ）小児科領域における医療上の有用性

①既存の治療法・予防法がない

②欧米の臨床試験において有効性・安全性等が既存の治療法・予防法と比べて明らかに優れている

③本邦で広範に使用され，用法・用量等を適正化することによる臨床現場への影響が大きい

表4　日本小児腎臓病学会におけるカテゴリー分け（表2のカテゴリーに対応）

2) 海外で承認されている臨床上不可欠な比較的古い医薬品で，国内に製剤がないもの
例：アミロライド，レバミゾール，クロラムブシル

3) 試薬を転用している医薬品，施設で化学合成している医薬品など
例：システアミン

5) 国内に同一有効成分及び同一剤型の医薬品はあるが，小児（あるいは特定の年齢群）の必要な適応（以下「新規適応」という）がないもの

（ア）小児（あるいは特定の年齢群）の他の適応はある（用量や安全性の評価がある程度されている）

① 成人や他年齢群でも新規適応がない
例：コハク酸メチルプレドニゾロンナトリウム（ネフローゼ症候群，ループス腎炎，急性進行性腎炎），デスモプレシン（夜尿症），ミゾリビン（頻回再発型ネフローゼ症候群）

（イ）小児（あるいは特定の年齢群）の他の適応もない

① 成人や他年齢群でも新規適応がない
例：沈降炭酸カルシウム（低カルシウム血症），ヘパリンナトリウム（慢性腎炎），ヒドロクロロチアジド，トリクロルメチアジド（尿細管性アシドーシス，高カルシウム血症），プレドニゾロン，メチルプレドニゾロン（慢性腎炎），カプトプリル，エナラプリル，リシノプリル，塩酸ベナゼプリル（慢性腎炎，腎保護作用，バーター症候群），ロサルタンカリウム，カンデサルタン，テルミサルタン，バルサルタン（慢性腎炎，腎保護作用），塩酸ジラゼプ（ネフローゼ症候群，IgA腎症以外の慢性腎炎），ジピリダモール（慢性腎炎），アザチオプリン，シクロホスファミド（ループス腎炎，ミコフェノール酸モフェチル，アスピリン，ワルファリンカリウム，ウロキナーゼ，塩酸オキシブチニン，塩酸フラボキサート，塩化ベタネコール，塩酸プロピベリン

② 成人や他年齢群では新規適応がある
例：沈降炭酸カルシウム（高リン血症）

6) 小児での安全性が確立していないもの，安全性の記載が不十分あるいは行過ぎているもので，保険で査定される可能性が比較的高い等の問題があるもの
例：インドメサシン，ヘパリンナトリウム，ワルファリンカリウム，アスピリン

表5　適応外使用に係る医療用医薬品の取扱いについて

研第4号　医薬審104号　平成11年2月1日

1. 医療用医薬品について，承認された効能または効果等以外の効能または効果等による使用にについて関係学会から要望がありその使用が医療上必要と認められ，健康政策局研究開発振興課より当該効能または効果等の追加等について検討するよう要請があった場合には，臨床試験等の実施及びその試験成績等に基づく必要な効能または効果等の承認事項一部変更承認申請を考慮すること．
2. 次に掲げる場合であって，臨床試験の全部または一部を新たに実施することなく，当該資料により適応外使用に係る効能または効果等が医学薬学上公知であると認められる場合には，それらを基に当該効能または効果等の承認の可否の判断が可能であることがあるので，事前に医薬安全局審査管理課に相談されたいこと．
   (1) 外国（本邦と同等の水準にあると認められる承認の制度またはこれに相当する制度を有している国（たとえば，米国）をいう．以下同じ．）において，すでに当該効能または効果等により承認され，医療における相当の使用実績があり，その審査当局に対する承認申請に添付されている資料が入手できる場合
   (2) 外国において，すでに当該効能または効果等により承認され，医療における相当の使用実績があり，国際的に信頼できる学術雑誌に掲載された科学的根拠となり得る論文または国際機関で評価された総説等がある場合
   (3) 公的な研究事業の委託研究等により実施されるなどその実施に係る倫理性，科学性及び信頼性が確認し得る臨床試験の試験成績がある場合

Clinical Practice）の合意などに基づき，医薬品の臨床試験の実施に関する省令（平成9年厚生省令第28号，GCP省令）が制定され，欧米と同等の治験の信頼性を確保するための基準が導入された．GCP省令の制定に伴い，治験の科学性，倫理性，信頼性を確保するため，治験の契約から実施に係る手続きが増加した．また，外国で実施された臨床試験データ受け入れが可能になったことなどにより，欧米で治験を実施する場合が増加し，いわゆる治験の空洞化ともいえる日本での治験離れが生じた．

この状況を改善すべく，平成15年4月に全国治験活性化3カ年計画を文部科学省と厚生労働省が共同で策定し，推進してきた．国内の治験届出数が増加傾向に転じたことなどより，治験の実施体制は改善し，日本で実施される体制が整備されつつあるものの，国際的なレベルからみると，治験のコスト，スピード，質においていまだ解決すべき課題があり，平成19年3月に新たな治験活性化5カ年計画を策定した．この事業では，10の治験中核病院と30の治験拠点医療機関が採択され，小児病院では，治験中核病院に国立成育医療センター，治験拠点医療機関に神奈川県立こども医療センター，大阪府立病院機構大阪府立母子保健総合医療センター，東京都立清瀬小児病院が含まれている．治験中核病院は，高度に専門的な知識や経験が要求されるなど，実施に困難を伴う治験などを計画・実施できる専門部門およびスタッフを有し，基盤が整備された病院をいう．治験拠点医療機関は，中核病院や他の拠点医療機関，地域の医療機関とも連携して治験などを円滑に実施できる体制を有する病院とされている．

むすび

日本での小児腎臓病領域における適応外使用状況は，小児科領域全体と変わりなく，また，小児科領域における適応外使用の背景については，根本的に欧米と日本で大きな違いはない．しかしながら，その対応策の検討および実施については，日本は欧米に比較して大きく遅れを取っているといわざるを得ない．欧米における小児治験の体制と推進策についてよく知ることは，日本の小児治験体制とその推進策を考えるために重要である．今後，日本の小児治験体制とその推進策を考える

際には，先行する欧米での対応策は大いに参考にすべきであるが，その経過をよく吟味し，日本の小児科の状況も充分に考慮した上で，適切な策を講じる必要がある．治験中核病院，治験拠点医療機関は治験の実施などにおいて中心的役割を担い，地域の医療機関とも連携して治験を円滑に計画，実施できる体制を整備する必要がある．

文献

1) Shirkey HC. Conference of Professional and Scientific Societies, Chicago. Commision on Drug Safety (sponsor); Chicago, Il; June 27-28, 1963.
2) 森田修之. 小児医薬品の用法・用量の実態と医薬品添付文書等との関連—内服薬について—. 厚生科学研究費補助金健康安全確保総合研究分野医薬安全総合研究事業「小児等の特殊患者群に対する医薬品の用法及び用量の確立に関する研究」平成13年度報告書（主任研究者: 大西鐘壽）. 2002.
3) 五十嵐隆. 研修医のための小児腎疾患の臨床. 東京: 診断と治療社; 1996.
4) 矢田純一, 柳澤正義, 山口規容子, 他. 今日の小児治療指針. 第12版. 東京: 医学書院; 2000.
5) 小児の治療指針. 小児科診療. 第65巻増刊号. 東京: 診断と治療社; 2002.
6) 白木和夫. 小児疾患の診断治療基準. 東京: 東京医学社; 1987.
7) 本田雅敬. 小児腎臓病における薬の適応外使用とその解決策. 日本小児科学会雑誌. 2008; 112: 8-14.
8) 本田雅敬. 小児腎疾患の適応外医薬品解消に向けての動きと教育. 日本小児臨床薬理学会雑誌. 2007; 20: 75-80.
9) 土田　尚. 日本小児臨床薬理学会が目指すもの. 日本小児科学会雑誌. 2007; 111: 959-66.
10) 土田　尚.「適応外使用」解決のための調査研究: 小児科領域. 厚生労働科学研究費補助金行政政策研究分野厚生労働科学特別研究「医薬品の適応外使用の適正化に関する調査研究」平成16年度報告書（主任研究者: 黒川　清）. 2004.
11) http://www.fda.gov/cder/pediatric/pediatric_rule1994.htm
12) http://www.fda.gov/cder/pediatric/
13) http://www.fda.gov/ohrms/dockets/98fr/120298c.pdf
14) http://www.fda.gov/cder/pediatric/S-650-PREA.pdf
15) 中村秀文. 医師主導の治験による小児への適応拡大. 薬事. 2005; 47: 1149-54.

CHAPTER 14

Japanese Perspective

HIDEFUMI NAKAMURA, MD, PhD

National Center for Child Health and Development, Tokyo 157-8535, Japan

SHUNSUKE ONO, PhD

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo 113-0033, Japan

INTRODUCTION

Off-label, extemporaneous, and/or unlicensed uses of drugs in Japanese children are common as in other parts of the world. After the implementation of ICH E11, the number of clinical trials in children appears to have increased only moderately. Japan does not have "pediatric regulations" equivalent to those in the United States or European Union (EU). Possible incentives for the industries involved in pediatric drug development have been extension of the reexamination period and preferential drug pricing, which appears to have limited effects.

The approval lag of new drugs in Japan has become a serious problem, and the Japanese government has been trying to establish new regulatory schemes to promote drug development in children. For important pediatric drugs that already have been developed in certain countries, the use of foreign data is accepted. The government is also making a tremendous effort to build a competitive environment for clinical trials and to speed up drug approval in the country. There is currently a pediatric clinical trial network being established with the National Center for Child Health and Development, which plays a central role. Discussion on additional regulatory measures to promote pediatric clinical trials is ongoing. With all the efforts combined, further improvements of pediatric drug development are expected in the near future.

PAST AND PRESENT STATUS OF OFF-LABEL, EXTEMPORANEOUS, AND UNLICENSED USE OF DRUGS IN JAPANESE CHILDREN

Off-Label Use of Drugs in Japanese Children

The off-label use of drugs in Japan has been very common, similar to other parts of the world. Morita[1] examined prescriptions of drugs covered by the National Health Insurance during

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1997 and 1998 for pediatric patients in four university hospitals and one affiliated general hospital. For outpatients and inpatients less than 18 years of age, 2032 drugs were prescribed on 531,137 occasions in one year. He and his colleagues examined the package inserts of these medications and found that only 495 drugs (24.4%) had sufficient information for pediatric dosage on the package inserts. Approximately 40% of these had the description "Safety is not established in children." Among these 2032 drugs, approximately 2% were either "contraindicated" or "not recommended in children" for certain age groups, although many of them are commonly used in daily practice. There were also ambiguous statements common in the labels, including "the dose can be adjusted accordingly for age" or no clear guidance on usage in children in approximately 20%. In the opinion of these authors, this situation has not changed over the last 10 years.

Extemporaneous Use of Drugs in Japanese Children

In 2005, Kato and colleagues[2] conducted a survey on the extemporaneous use of drugs in children at 32 Japanese institutions including 18 children's hospitals. All extemporaneous uses of pediatric drugs during the 4-week period from October 17, 2005 to November 13, 2005 were reported. There were a total of 1666 incidences of dosage form changes. In 1227 incidences, age appropriate powders were made either by crushing tablets and/or adding sucrose to make different strengths. On many occasions, Japanese children have powders orally administered as they are or after adding a small amount of water to make them paste-like. This obviously is the reason why the dosage form changes to powder are so common. Most Japanese pharmacies have machines to automatically divide powder evenly and to pack it in sachets.

In 176 cases, tablets were divided into two or more sections; in 50 cases, syrups/suspensions were made from other forms including intravenous solutions (e.g., midazolam for sedation). In 40 cases, the suppositories were cut for appropriate dosages, and in 23 incidences, inhalation solutions were made from other forms including intravenous solutions. The top 10 drugs for dosage form changes on prescription number basis were warfarin potassium, methyl digoxin, enalapril maleate, dantrolene sodium, lisinopril, beraprost sodium, hydrocortisone, baclofen, chloral hydrate, and propranolol hydrochloride.

Unlicensed Pediatric Drugs in Japan

According to the survey by the Japanese Society for Inherited Metabolic Diseases in 2006, "raw" chemical compounds including sodium benzoate, betaine, cysteamine, and glycine are dispensed for certain orphan diseases. Among these, betaine and cysteamine are already approved in some countries, and the Ministry of Health, Labour and Welfare (MHLW) has been seeking for industries that are interested in developing these drugs in Japan following the procedures recommended by the Study Group on Unapproved Drugs.

Patients or physicians may have to import medications, which do not exist in Japan as approved drugs. Especially for patients with oncology and genetic diseases, who have to pay, the cost for these medications can often be more than US $10,000 annually/person. These problems with unlicensed medicines and approval lag (drug lag) have become a focus of social attention, especially in 2004 when the former prime minister, Junichiro Koizumi, ordered the associated cabinet members to take action to improve access to unlicensed medicines and innovative equipment. Approval lag or drug lag is the lag between the time when a drug has been approved in the country and the time when the drug was first approved in another part of the world.

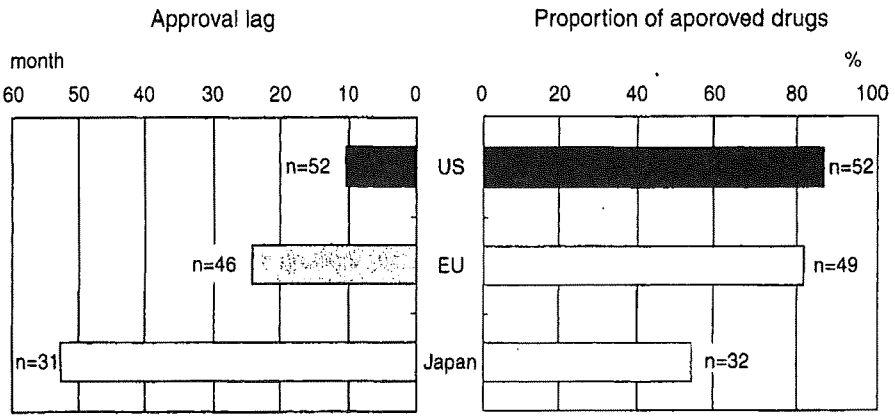

FIGURE 14.1 Proportion of approved drugs and mean approval lag of 60 orphan drugs in the United States (U.S.), Eruopean Union (EU), and Japan. Approval lag was calculated for the approved drugs in each region for which data were available.

Tsuji and Tsutani[3] examined the approval status of the new chemical entities (NCEs) in the United States, EU, and Japan between 1999 and 2005. Out of 334 NCEs approved at least in one of the three regions, 274 (82.6%) were approved in the United States, 262 (78.4%) in the EU, and 181 (54.2%) in Japan. The mean approval lag was 13.5 months in the United States, 13.2 months in the EU, and 46.3 months in Japan. Figure 14.1 shows the mean approval lag and proportion of approved drugs of 60 NCEs designated as orphan drugs (except for anti-HIV drugs). Japan had the lowest number of approvals (32 NCEs or 53.3%) and longer mean approval lag (52.6 months) when compared to the United States or EU.

In this survey, they also examined the development status of unapproved drugs (Figure 14.2a) and unapproved orphan drugs (Figure 14.2b) as of October 31, 2006.

For the NCEs in which they could find the development status, approximately 50% of the total unapproved NCEs in Japan were not under development, whereas 78.6% (22 NCEs)

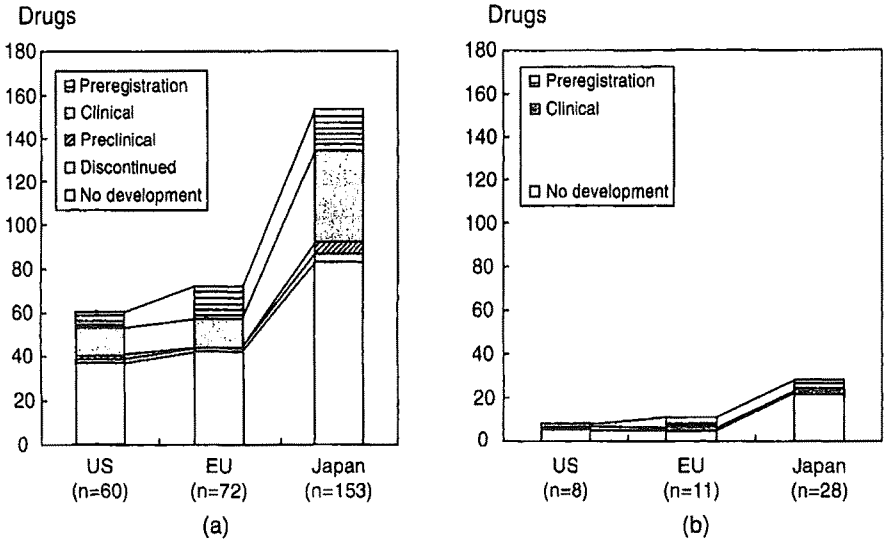

FIGURE 14.2 Development status of unapproved NMEs in the United States (U.S.) European Union (EU), and Japan: (a) for all the unapproved NMEs for which data were available and (b) for all the unapproved NMEs designated as orphan drugs for which data were available.

were not under development as orphan drugs (personal communication). It is believed that one of the reasons why a higher percentage of orphan drugs were left out of the development process is that fewer venture companies are involved in orphan drug development in Japan compared to the United States and EU and there is insufficient support to nourish venture companies in Japan. The need for support for venture companies for drug and device development is considered to be one of the major aims of the 5-year strategy for developing innovative drugs and devices.

Impact of Off-Label, Extemporaneous, or Unlicensed Use of Drugs in Japanese Healthcare

Japan has a nationwide healthcare insurance system, and all the citizens are insured and receive medical services at any time at any institution. For pharmaceutical products, the reimbursement is strictly based on the conditions of approval (i.e., indication(s), dose, regimen, and patient types) under the Pharmaceutical Affairs Law (PAL), the primary law governing drug development in Japan. The Japanese insurance bodies are not allowed to make their own decisions on reimbursement, which is in marked contrast to the diversified decisions by the U.S. insurance bodies. The Japanese healthcare insurance system also does not allow the use of uninsured drugs in combination with the insured practice. If physicians want to use uninsured drugs, the Japanese healthcare insurance system does not cover any of the costs of the medical care during that particular hospital visit.

Off-label, extemporaneous, or unlicensed use of drugs also may mean that the patients who experienced adverse effects cannot receive relief from the Adverse Health Effect Relief Service[4] by the Pharmaceutical and Medical Devices Agency (PMDA). It is also believed that there is significant underreporting of adverse events of off-label, extemporaneously used, or unlicensed drugs.

INVOLVEMENT OF THE JAPAN PEDIATRIC SOCIETY (JPS) FOR FACILITATION OF PEDIATRIC DRUG DEVELOPMENT

The Members of the Committee on Drugs of the JPS organized a working group to study the approval status of pediatric drugs in 1998 as part of the MHLW supported research. Representatives of 17 pediatric subspecialty societies joined the working group and gathered information on off-label drugs, which need to be labeled. The list for these drugs is called the "priority list" and has been used for the selection of drugs for the evaluation by the Study Group on Pediatric Drug Therapy. Some of the working group members have also been involved in setting up the infrastructure for clinical trials in certain areas including neonatology and pediatric nephrology.

The working group also started to accumulate information on unlicensed drugs, which need to be approved urgently in the country. After the drugs are listed, associated pediatric subspecialty societies are responsible to submit request letters to the MHLW for evaluation by the Study Group on Unapproved Drugs.

The Committee also has been involved in several activities to facilitate clinical trials, drug development, and the approval process. For example, at a public hearing in December 2006, the Committee gave requests to the Study Group on Faster Access to Innovative Drugs to consider several issues including the following:

1. Establishment of certain legal obligations for the industry to conduct clinical trials in a timely manner on important pediatric drugs.
2. Appropriate measures to hasten and strengthen the NDA review process for pediatric drugs by the PMDA.
3. Stronger incentives for industry partners to collaborate and more effectively develop opportunities for pediatric drug development.
4. Reinforcement of post market surveillance in cooperation with the JPA.

PAST AND PRESENT GUIDANCES AND NOTIFICATIONS FOR PEDIATRIC DRUG DEVELOPMENTS IN JAPAN

The primary law governing drug development in Japan is the PAL. There are also regulations that set forth the general principles governing drug development and their specific implementing procedures.[5] There are still no regulations equivalent to the U.S. Best Pharmaceuticals for Children Act, the U.S. Pediatric Research Equity Act, or the EU Paediatric Regulation. This section describes the past and present guidances and ordinances for pediatric drug development in Japan.

Impact of ICH E11

Until the implementation of the ICH E11 guideline, "Clinical Investigation of Medicinal Products in the Pediatric Population," in December 2000, there had been no official guideline for pediatric drug development in Japan. After the implementation, the importance of pediatric clinical trials seems to have been recognized more among industry partners and academia, but the number of pediatric clinical trials seems to have increased only moderately. Levy-Petalinkar and Campen discuss these same issues in the United States as presented in Chapter 7 in this book.

Nakagawa reviewed the evaluation reports issued by the PMDA and its former division, the Pharmaceutical and Medical Devices Evaluation Center (PMDEC), from April 2001 to January 2007, for drugs approved under the PAL (pers. comm.). Among 188 new indications between April 2001 and June 2004, 28 (14.8%) included pediatric indications. For these 28 indications, domestic clinical trials were performed for only 10 (35.7%). Among 139 approvals between July 2004 and January 2007, 25 approvals (18.0%) included pediatric indications. For these 25 indications, domestic clinical trials were performed for 18 indications (72.0%). This suggests that the total number of clinical trials in children may have increased recently.

The Official Notification Describing Procedures for Approval of Off-Label Drugs

This ordinance is classified as Kacho-tsuchi, subministerial division notification that is sometimes translated as "guideline."[6] This notification was issued jointly by the Evaluation and Licensing Division (ELD), the Pharmaceutical and Medical Safety Bureau, and the Research and Development Division (RDD), Health Policy Bureau, MHLW.

According to this notification, the RDD will encourage the company to consider pursuing a clinical development strategy for expansion of the already approved indication(s), in cases

where there is a formal petition from the academic society to consider an approval AND a recognized medical necessity for the indication. When certain conditions are met, this notification allows off-label indications to be approved with only a literature-based application, waiving some or all domestic registration-directed clinical trials (Chiken), which usually are necessary. If this appears to be a possibility, consultation with the ELD prior to the application submission is recommended. The following are the three situations when domestic Chiken may be waived:

1. The proposed indication has already been approved in a foreign country, which has an equivalent drug approval system to Japan (e.g., the United States and EU), and there is a sizable body of data accumulated from clinical practice. If this is the situation, and the material submitted to the overseas approving authority can be submitted according to the Japanese requirement, domestic Chiken may be waived.
2. In cases when the indication has been approved according to the conditions stipulated above, a sizable body of data from use in clinical practice has been accumulated, AND reliable results are published in internationally recognized journals. To meet this standard, the data should be of high scientific quality.
3. In cases when there exists scientifically reliable data from studies conducted under the auspices of a publicly sponsored organization such as the MHLW. To meet this standard, such studies must have been conducted in accordance with currently accepted international ethical and scientific standards.

According to Nakagawa, among 22 new pediatric indications approved between April 2001 and June 2004, 10 drugs were approved based on this notification without Chiken. Between July 2004 and January 2007, 3 out of 25 approvals of new pediatric indications were based on this notification.

Extension of the Reexamination Period

Extension of the reexamination period was introduced when the revision of the MHLW ordinance on postmarketing surveillance was made in December 2000. In Japan, the reexamination period is applied to all newly approved indications and this was usually 6 years when this "incentive" was introduced. The usual reexamination period was extended to 8 years in April 2007. Data protection is applied during the reexamination period. When a company conducts clinical trials for a pediatric indication during the reexamination period, the reexamination period is extended up to 10 years. This extension is intended to cover the clinical trial period with the reexamination period. It turned out that industries only benefit when their drugs can get a longer reexamination period compared to the patent period. It does not benefit the industry partner whose drug patent period is much longer than the reexamination period.

Ironically, this extension of the reexamination period, which is considered to be an incentive for industry, actually may delay the pediatric drug development process. Based on examination of recent evaluation reports from the PMDA, it appears that many industry partners start postmarketing clinical trials for pediatric indication just before the expiration of the reexamination period so that they can get an extension to cover the clinical trial period. If the industries start the clinical trials too early, they may not get the extension of the reexamination period.

RECENT GOVERNMENT EFFORTS TO INTRODUCE NEW DRUGS TO JAPAN

Many drugs already marketed in the United States and EU are not introduced in Japan for several reasons. Even when they are finally introduced in Japan, it is quite common that there is a significant approval lag in the market introduction. Especially in cancer therapy, the fact that many drugs and therapeutic regimens already approved in Western countries were unavailable or not approved in Japan has caused Japanese policymakers to establish regulatory schemes to bring these drugs to Japan. Lack of domestic approvals in a significant number of drugs and regimens for pediatric treatments has also become a national concern, and there are ongoing MHLW activities to resolve the off-label use and unlicensed use of drugs in children. The information described here is current as of October 2008.

Study Group on Unapproved Drugs (MHLW, January 2005)

This study group started in January 2005 to oversee the situation of the approval lag, to evaluate the need to introduce unapproved drugs in Japan, and to lead them to the clinical development stage. Eighteen formal meetings have been held since its establishment, and development and approval strategies for 43 drugs have been discussed. Of the 43 drugs, 22 are oncology drugs and 15 are pediatric drugs.

The study group also recommends that clinical trials for safety confirmation should be performed for some drugs for which a New Drug Application (NDA) has already been submitted, because such trials could provide opportunities for patients to access these drugs during the NDA review. Compassionate use of investigational or unapproved drugs has not been legitimized in Japan but has been discussed for possible introduction into Japan by the Study Group on Faster Access to Innovative Drugs.

Study Group on Cancer Combination Therapy (MHLW, January 2004 to February 2005)

This study group specifically focused on off-label indications or unapproved regimens of cancer drugs for which Japanese approval was already obtained for some other indication(s) or regimen. To fill the gap between Japan and the United States/EU, this MHLW study group investigated the current Japanese situation and collected clinical evidence available in foreign countries. When the investigation showed that a given drug use was considered "standard" in the therapeutic field, then the MHLW issued approval based primarily on those prior investigations and foreign evidence. In 2005, expanded indications were approved for 30 cancer drugs including 6 pediatric drugs for rhabdomyosarcoma, Ewing's sarcoma, and neuroblastoma.

Committee for Vaccine Industry Vision (MHLW, March 2007)

The objective of the committee is to establish nationwide vaccination programs that are effective and efficient and draw investment in vaccine development from drug companies that are generally hesitant to develop new vaccines because of the very small market size for vaccine products. Due to increasing concerns for possible future pandemics of new type flu viruses, however, the MHLW considers it critical to have an appropriate level of

manufacturing capacity for vaccine products in Japan. Activities of this committee will enhance introducing vaccines available in foreign markets.

Study Group on Pediatric Drug Therapy (MHLW, March 2006)

Using the similar scheme of the Study Group on Cancer Combination Therapy, the Study Group on Pediatric Drug Therapy focuses on a solution for the off-label use of pediatric drugs. A list of 99 drugs chosen from the JPS "priority list" was submitted to the study group by pediatric subspecialty societies, and so far 8 drugs have been chosen to be evaluated. The study group investigates the approval status and related information in the United States, United Kingdom, France, and/or Germany, the current Japanese situation, and other clinical evidence available in the literature. When the investigation shows that a given drug use is considered to have "sufficient evidence" for the indication and/or dosage, then the MHLW issues approval based on those investigations and foreign evidence supporting the claim. As of October 2008, expanded indications/dosages have been approved for all the pediatric formulations of acetaminophen, which had rather limited indications and dosage before (e.g., no indication for pain, once daily for suppository). Evaluation of methotrexate and bolulinum toxin type A have been completed, and there is ongoing investigation of the remaining 5 drugs (i.e., flecainide, methylphenidate, ciprofloxacin, cyclophosphamide, and acyclovir). It is most likely that investigation of other drugs will be initiated in the near future.

Compared to 30 cancer drugs approved in 2 years, the progress of this study group has been rather slow. One of the reasons is that there are very scarce published data on the off-label use of drugs in Japan, and it takes some time to gather reliable information on the current status of off-label use. Even after completing the survey on current status, it sometimes becomes clear that there is some discrepancy between the commonly prescribed dose and/or indication in Japan and the approved dose and/or indication in the four foreign countries. Lack of appropriate pediatric formulations for many drugs also can be an obstacle for the forthcoming evaluations. For now, there is minimal or no incentive for the industries to produce new formulations for children, and it will be extremely difficult to have the industry develop new formulations based on the current scheme of the study group.

Drug Pricing for Pediatric Drugs

The best incentive for industries for pediatric drug development is believed to be increasing drug prices. In 2006, preferential drug pricing for pediatric drugs was newly introduced, although the increase of the price was merely 3–10% and only for drugs that have no other pharmacologically similar drugs on the market. In 2008, increase of the drug pricing has further changed to 5–20% and is for drugs whose similar drugs have no preferential pricing. As many off-label drugs have been on the market a long time, and drug prices decrease every year, the drug prices for adult indications of these off-label drugs are cheap. For these kinds of drugs, a 5–20% increase may be too small for industry as an incentive.

Japan does not have "flat price" in the marketplace, and drug prices generally get cheaper, especially drugs used in children smaller than 20 kg. The prices for pediatric dry syrups are generally set to make the price for a 20-kg child equivalent to the price for an adult dose. This rule may become an obstacle when a certain drug is expected mostly to be used in small children.

GOVERNMENT EFFORTS TO PROMOTE CLINICAL TRIALS IN JAPAN

The MHLW and related government agencies have been implementing strategies to boost the number and quality of Japanese clinical trials in the last few years. The outcome of these strategies is expected to be seen in the near future.

Sponsor-Investigator Trials

The revision of PAL in 2002 enabled physicians to conduct sponsor-investigator trials in Japan for the first time. The Committee on Drugs of JPA recommends that JPA members become actively involved in sponsor-investigator trials and utilize them to set up a stronger infrastructure for pediatric clinical trials. There have been seven clinical trials conducted or scheduled.

In August 2007, expanded indication for the use of fentanyl citrate in children including neonates was approved as the first drug ever studied by the sponsor-investigator trials in the country. The drug was contraindicated for 2 year olds and younger children prior to this period. One other clinical trial was completed, another trial is still ongoing, and three more trials started as of October 2008.

Three-Year Clinical Trial Promotion Plan (MHLW and MEXT, 2003–2005)

The MHLW and the Ministry of Education, Culture, Sports, Science and Technology (MEXT) jointly executed a set of programs to promote Japanese clinical trials. Setting up several large networks for clinical trials was one of the important objectives of this plan. Research grants to establish networks and implement some sponsor-investigator trials as model programs were managed by the Center for Clinical Trials of the Japan Medical Association. As of October 2008, there were more than 1400 clinical institutions registered for the networks. Training programs for clinical research coordinators (e.g., research nurses, pharmacists) were provided regularly under this plan. Several symposia were also held to raise public awareness of clinical trials. It is believed that Japanese patients are not necessarily interested in clinical trials, because they can afford medical services without substantial financial burdens.

The national hospitals and research centers directly managed by the MHLW have been promoting harmonization of trial contract documents. These streamlining efforts also are intended to reduce the administrative costs of trials.

New Five-Year Clinical Trial Promotion Plan (MHLW and MEXT, 2007–2011)

In March 2007, the MHLW and MEXT published the 5-year promotion plan that follows the previous 3-year plan. The new plan aims to create several large networks of clinical institutions. Each network has a core hospital that orchestrates the operations with its affiliated hospitals. The MHLW chose 10 core and 30 affiliated major hospitals, based on regional and therapeutic needs as well as their performance in clinical trials. The aim and role of the network of core and affiliated major hospitals described by the MHLW is shown in Figure 14.3.

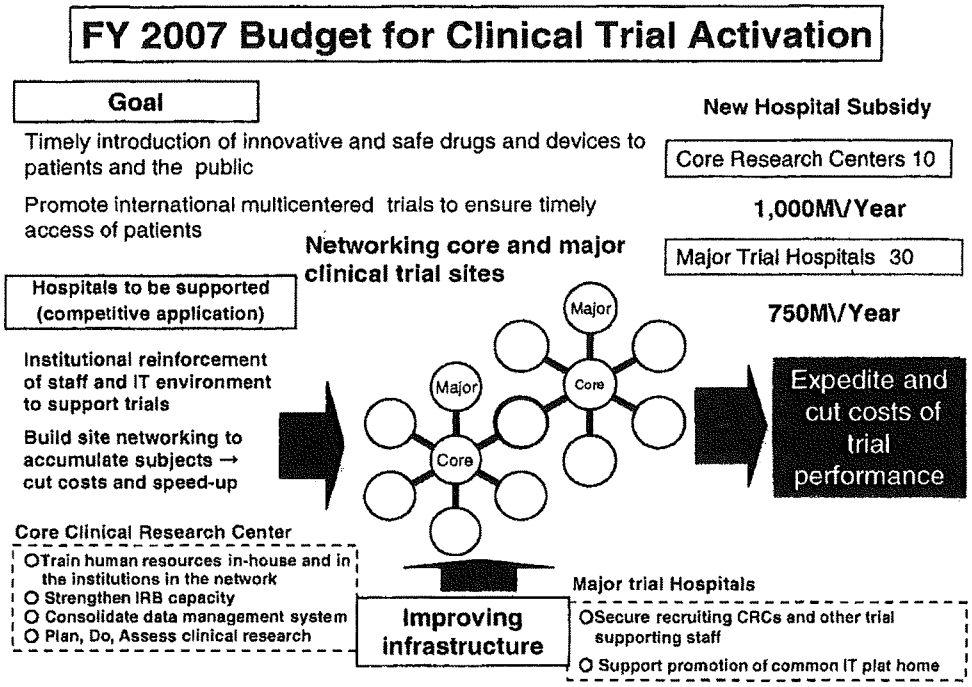

FIGURE 14.3 Role of the network of core and affiliated major hospitals explained by the R&D Division, MHLW.

For a clinical trial network for pediatric drugs, the National Center for Child Health and Development (NCCHD) has been chosen as the core hospital, and the Kanagawa Children's Medical Center, the Osaka Medical Center and Research Institute for Maternal and Child Health, and the Tokyo Metropolitan Kiyose Children's Hospital were chosen as affiliated major hospitals. Networking with other children's hospitals is also expected, and the above four hospitals are to play a major role in conducting networked clinical trials in children.

According to this new 5-year plan, training programs for investigators, research nurses, and pharmacists are provided in more intensive forms than in the previous 3-year plan. In addition, the network hospitals can afford to employ staff, including research nurses, pharmacists, biostatisticians, and data managers through budgetary supports. To attract more industry sponsors, the MHLW promises to remove administrative red tape and streamline operations in the networks, including adoption of information technology. Decrease in the costs of clinical trials is also an alleged goal of the plan. To achieve that goal, however, various factors in addition to costs of clinical trials must be taken into consideration because prices are determined not only by cost components but also by market structure and monopoly, if present.

Study Group on Faster Access to Innovative Drugs (MHLW, 2006–2007)

The MHLW convened an expert panel to discuss the bottlenecks to the introduction of new drugs in Japan in October 2006. This study group focused on the principles of new drug

approval, postmarketing safety measures, and enhancement of the PMDA review. It is expected that the results of this will be reflected in upcoming amendments of existing regulations.

In the final report of this study group, issued in July 2007, it is specified that the government should consider stronger incentives for industry and other regulatory measures to facilitate pediatric drug development. It is believed that this statement is in response to the request from the Committee on Drugs of JPA at the public hearing.

"Innovation 25" Strategic Council (Cabinet Office, 2006)

Former Prime Minister Shinzo Abe launched a long-term innovation strategy guideline in his inaugural policy speech in September 2007. The guideline, called "Innovation 25," specifically emphasizes the need to concentrate on several technology areas essential for the solid economic growth of Japan in the coming decades, and pharmaceutical R&D by the drug industry and clinical researchers are regarded as key areas. The Innovation 25 Strategic Council plays the central role in further planning and implementing detailed strategies.

Five-Year Strategy for Developing Innovative Drugs and Devices (MHLW, MEXT, and METI, 2007–2011)

Three ministries made this strategy: the MHLW, Ministry of Education, Culture, Sports, Science and Technology (MEXT), and the Ministry of Economy, Trade and Industry (METI). The major goals of this strategy are to reinforce clinical research infrastructure to ensure safe and secure patient access to new drugs and devices; that is, (1) institutional infrastructure building for core clinical research centers' networks, (2) human resource development for clinical research, and (3) regulatory research promotion and approval system reform. Furthermore, MHLW is planning to establish "medical research clusters" at National Centers in 2008, to accelerate and promote research and development and new partnership with industry. According to this plan, the NCCHD will become involved in establishing the medical research clusters for pediatric drug developments.

PROSPECT FOR THE NEAR FUTURE

Japan has no strong "stick-and-carrot" approach for industry to conduct pediatric clinical trials as the United States and the EU have recently adopted. The Committee of Drugs of JPA will be taking further actions to have governments consider setting up new regulations to promote pediatric drug trials. The MHLW or PMDA does not have the authority to control the patent period. Therefore, the Japanese government may have to consider other incentives, including preferential drug prices, taxation, and fast track review.

As described in this chapter, the Japanese government is taking several critical actions to promote pediatric drug development. The Japan Pharmaceutical Manufacturers Association also has a task force to work on this issue. With all these efforts combined, we are expecting that further promotion of pediatric drug development will occur in the near future.

REFERENCES

1. Morita S. Prescription and package insert description analysis in pediatric drug use (in Japanese). In: *1999 MHLW Project Report for the Research on Current Status of the Off-Label Use of Drugs in Children and Possible Solutions* (PI: Onishi S); 2000: 52–99.
2. Kato Y, Ishikawa I, Kushida K, Nakamura H. Survey of pediatric dosage form changes in pediatric drug therapy Japan. *Paediatric and Perinatal Drug Therapy* 2008.
3. Tsuji K, Tsutani K. Approval of new chemical entities in the US, EU and Japan (in Japanese). *Iryo to Shakai [J Health Care Soc].* 2007;17(2):243–258.
4. Website for the Adverse Health Effect Relief Services. Available at http://www.pmda.go.jp/english/healtheffect.html.
5. Ono S. Ministry of Health, Labour and Welfare (MHLW, Japan). In: D'Agostino RB, Sullivan L, Massaro JM, eds. *Wiley Encyclopedia of Clinical Trials.* Hoboken, NJ: John Wiley & Sons; 2007.
6. Fujiwara Y, Kobayashi K. Oncology drug clinical development and approval in Japan: the role of pharmaceuticals and medical devices evaluation center (PMDEC). *Crit Rev Oncol/Hematol.* 2002;42:145–155.

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ORIGINAL ARTICLE

Cyclosporine and steroid therapy in children with steroid-resistant nephrotic syndrome

Yuko Hamasaki · Norishige Yoshikawa · Shinzaburo Hattori · Satoshi Sasaki · Kazumoto Iijima · Koichi Nakanishi · Takeshi Matsuyama · Kenji Ishikura · Nahoko Yata · Tetsuji Kaneko · Masataka Honda · for Japanese Study Group of Renal Disease in Children

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Abstract We conducted a prospective, multicenter trial to evaluate the efficacy and safety of a 12-month course of cyclosporine in children with steroid-resistant nephrotic syndrome (SRNS). Thirty-five patients were enrolled, of whom 28 had minimal change or diffuse mesangial proliferation (MC/DMP), and seven had focal segmental glomerulosclerosis (FSGS). All patients received cyclosporine and prednisolone; patients with FSGS additionally received methylprednisolone pulse therapy (MPT). The dose of cyclosporine was adjusted to maintain a trough level of 120–150 ng/ml during the initial 3 months of treatment, followed by 80–100 ng/ml during months 4–12. The primary end point was the remission rate at month 12. Remission was achieved in 23 of 28 (82.1%) patients in the MC/DMP group and in six of the seven (85.7%) patients in the FSGS group. Follow-up renal biopsies were performed in 26 patients (nine at month 12, 17 at month 24), and cyclosporine-related nephrotoxicity was detected in one (3.8%). Major adverse events comprised severe bacterial infections (two patients) and posterior reversible encephalopathy syndrome (one patient). In conclusion, a high remission rate was achieved in our patient cohort using a combined cyclosporine/prednisolone treatment regimen in children with SRNS who had MC/DMP and a combined cyclosporine/prednisolone plus MPT regimen in children who had FSGS.

Keywords Children · Clinical trial · Cyclosporine · Methylprednisolone · Nephrotic syndrome · Steroid-resistant

Y. Hamasaki (✉) · K. Ishikura · N. Yata · M. Honda
Department of Pediatric Nephrology,
Tokyo Metropolitan Kiyose Children's Hospital,
1-3-1 Umezono,
Kiyose-city, Tokyo 204-8567, Japan
e-mail: yu.hama@chp-kiyose-tokyo.jp

N. Yoshikawa · K. Nakanishi
Department of Pediatrics, Wakayama Medical University,
Wakayama, Japan

S. Hattori
Department of Fundamental Medicine,
Kumamoto Health Science University,
Kumamoto, Japan

S. Sasaki
Department of Pediatrics,
Hokkaido University Graduate School of Medicine,
Sapporo, Japan

K. Iijima
Department of Pediatrics,
Kobe University Graduate School of Medicine,
Kobe, Japan

T. Matsuyama
Department of Pediatrics, Fussa Hospital,
Tokyo, Japan

K. Ishikura · N. Yata
Department of Clinical Research,
Tokyo Metropolitan Kiyose Children's Hospital,
Tokyo, Japan

T. Kaneko
Department of Biostatistics/Epidemiology
and Preventive Health Sciences, School of Health
Sciences and Nursing, Graduate School of Medicine,
the University of Tokyo,
Tokyo, Japan

Abbreviations

DMP	diffuse mesangial proliferation
FSGS	focal segmental glomerulosclerosis
MC	minimal change
MPT	methylprednisolone pulse therapy
PRES	posterior reversible encephalopathy syndrome
SRNS	steroid-resistant nephrotic syndrome

Introduction

Steroid-resistant nephrotic syndrome (SRNS) is the most common glomerular disease in children that progresses to end-stage renal failure [1]. After a follow-up of 10 years, end-stage renal failure develops in 30–40% of children with SRNS [2, 3].

Despite many clinical trials, the optimal treatment regimen for children with SRNS remains unclear. The Cochrane analysis of randomized and controlled prospective trials of SRNS revealed that remission rates after cyclosporine pharmacotherapy were significantly higher than those after other immunosuppressive agents [4]. Cyclosporine has recently been designated as a first-line treatment for SRNS in children [4–6]. Randomized controlled trials have shown that children with SRNS who have completed a 6-month course of cyclosporine have a significantly increased rate of complete remission compared to those treated with placebo [7] or supportive therapy [8]. The efficacy of cyclosporine for SRNS has also been evaluated in many other single-center trials [1, 5, 9–13]. Niaudet et al. and others have reported that cyclosporine combined with alternate-day or low-dose steroids produces a higher response rate than cyclosporine monotherapy [5, 10, 14, 15]. Several studies have reported a favorable response to methylprednisolone pulse therapy (MPT) in patients with focal segmental glomerulosclerosis (FSGS) [16–19].

We have conducted a prospective, multicenter trial to evaluate the efficacy and safety of a 12-month course of cyclosporine-based treatment in children with SRNS. All patients received cyclosporine and prednisolone. Patients with FSGS additionally received MPT because steroid-resistant FSGS is associated with poor outcomes [2, 3, 20].

Methods

Patients

To be eligible for enrollment, patients had to have SRNS (see Definitions). The pathological diagnosis was established by renal biopsy and was classified into three groups: minimal change (MC), diffuse mesangial proliferation (DMP), and FSGS. At study entry, the pathological findings were evaluated by a pathologist at each hospital. Patients aged 1–18 years were eligible for enrollment.

Patients were excluded if they had: (1) previously received MPT or immunosuppressive agents, (2) clinically significant hematuria, (3) uncontrolled hypertension, (4) severe liver dysfunction, (5) serious infection, or (6) impaired renal function (creatinine clearance <60 ml/min per 1.73 m^2). Patients who had FSGS with more than 20% global sclerosis were also excluded.

The study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki Principles, and informed consent was obtained from all patients or their parents.

Definitions

Nephrotic syndrome was diagnosed if the urinary protein/creatinine ratio was ≥1.8 and the serum albumin level was ≤2.5 g/dl. SRNS was diagnosed if no remission (serum albumin level ≤2.5 g/dl) was achieved after treatment with 2 mg/kg prednisolone daily for 4 weeks.

The response to treatment was classified as complete remission, partial remission, or non-remission. Complete remission was defined as negative or trace proteinuria (on the dipstick method or a urinary protein/creatinine ratio ≤0.20) on urinalysis and a serum albumin level of >2.5 g/dl. Partial remission was defined as a serum albumin level of >2.5 g/dl, but persistent proteinuria on urinalysis. In the present trial, remission was defined as complete remission and partial remission. Non-remission was defined as persistent nephrotic syndrome.

The relapse of nephrotic syndrome in patients who once achieved complete remission was defined as the reappearance of proteinuria (2+ on the dipstick method) for 3 consecutive days. The relapse of nephrotic syndrome in patients who once achieved partial remission was defined as increased proteinuria and a serum albumin level of ≤2.5 g/dl. Frequently relapsing nephrotic syndrome was defined as three relapses within any 6-month period or four or more relapses within any 12-month period.

Late non-response to steroids was defined as an initial response to steroid therapy but not during a subsequent relapse.

Protocol treatment

All patients received oral cyclosporine (Neoral; Novartis, Basel, Switzerland) divided into two equal daily doses plus prednisolone. The total duration of treatment was 12 months, and the follow-up period was 12 months. The dose of cyclosporine was adjusted to maintain a whole-

blood trough level of 120–150 ng/ml for the initial 3 months, followed by 80–100 ng/ml for months 4–12. Prednisolone was given in a dose of 1 mg/kg per day, divided into three equal daily doses for the first 4 weeks, followed by a reduced dose of 1 mg/kg every other day in a single dose for months 2–12. Patients with FSGS additionally received methylprednisolone by intravenous infusion in a dose of 30 mg/kg per day (maximum prescribed amount 1 g) for 3 consecutive days at weeks 1, 2, 5, 9, and 13 (Fig. 1).

The response to treatment was evaluated at the end of month 4 of the protocol treatment. In patients who achieved complete remission or partial remission, treatment was continued until month 12. For patients with MC or DMP (MC/DMP) who did not achieve remission within 4 months, treatment was restarted with the regimen of the FSGS group (cyclosporine, prednisolone, and MPT). Patients with FSGS who did not achieve remission within 4 months were given off-protocol treatment chosen at the discretion of the physician. Patients who progressed to SRNS or frequently relapsing nephrotic syndrome after once achieving remission also received off-protocol treatment.

At the completion of the protocol treatment, the dose of cyclosporine was tapered by 0.5–1.0 mg/kg per day every week, and all patients were scheduled to undergo renal biopsy. An independent investigator at the coordinating center who was blinded to patients' information also reviewed the histological sections. Arteriolar changes, tubular atrophy, and interstitial fibrosis were graded semiquantitatively according to a scale of 0 to 3+ as follows: 0, none; 1+, mild; 2+, moderate; 3+, intense. A diagnosis of cyclosporine-related nephrotoxicity required arteriolopathy (arteriolar hyalinosis, hyperplasia) with or without striped interstitial fibrosis and tubular atrophy.

Concomitant treatment with drugs known to affect the pharmacokinetics of cyclosporine was avoided. Antihypertensive drugs (calcium-channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers), diuretics (furosemide), anticoagulants, and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) were permitted.

Treatment for relapses of nephrotic syndrome

Patients who had relapses of nephrotic syndrome after achieving complete remission or partial remission received 2 mg/kg per day of prednisolone in three divided doses (maximum dose 80 mg/day). For patients who responded to prednisolone, the dose was reduced to 2 mg/kg in a single dose every other day for 2 weeks after 3 consecutive days of negative proteinuria on the dipstick method, followed by 1 mg/kg in a single dose every other day until the end of month 12.

Pretreatment evaluation and follow-up

The following measurements and tests were performed at baseline, after 2 weeks, after 1 month, and every month thereafter: body weight and height; blood pressure; blood analysis (complete blood cell count, blood chemistry); urine tests (urinalysis, quantitative proteinuria); estimated creatinine clearance as determined by the Schwartz equation. The trough level of cyclosporine was measured by monoclonal radioimmunoassay.

The primary end point was the remission rate at month 12. The secondary end point was the remission rate at month 4, change in renal function, and adverse events.

Recommended treatment

Since May 2003, the Safety Committee has recommended that for patients who completed the 12-month protocol

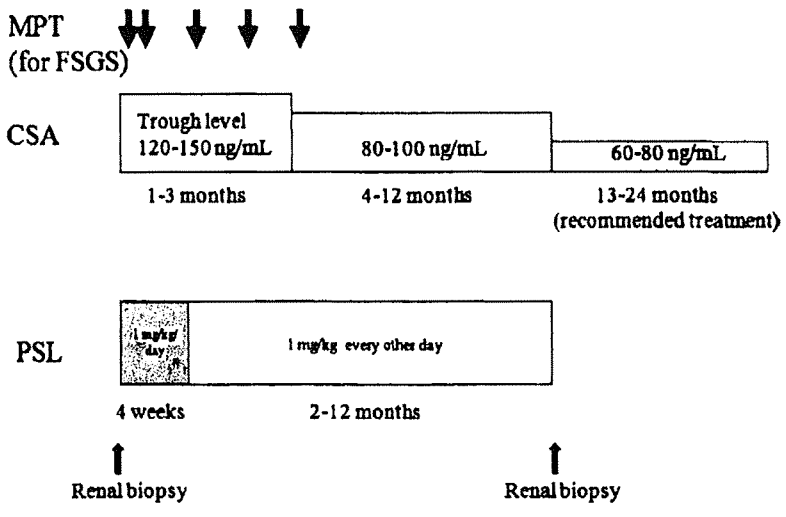

Fig. 1 Protocol for patients with steroid-resistant nephrotic syndrome. *FSGS* Focal segmental glomerulosclerosis, *MPT* methylprednisolone pulse therapy, *CSA* cyclosporine, *PSL* prednisolone