The North American Immune Tolerance Registry: Practices, Outcomes, Outcome Predictors

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Keywords
Hemophilia A, hemophilia B, inhibitor therapy, immune tolerance

Summary

The North American Immune Tolerance Registry was initiated to study of immune tolerance (ITT) in Canada and the United States with respect to: 1) therapeutic regimens in use for haemophilia A (HA) and B (HB) inhibitor patients; 2) therapeutic outcomes; 3) potential predictors of successful outcome and 4) complications of therapy. Data on 188 ITT courses was collected by questionnaire from 60 haemophilia centers from 1993-99. Among the completed courses, the overall ITT success rate was 70% (115/164) for all HA and 31% (5/16) for all HB. Outcome parameters noted to be predictive of ITT success for all HA were 1) pre-ITT induction (p = 0.003), 2) ITT peak (p = 0.007) and 3) historical pre ITT peak (p = 0.04) inhibitor titres. An inverse correlation between total daily dose (units/kg/day) and success: (80% with under 50; 71% with 50-99; 73% with 100-199; and 41% with ≥ 200, p = 0.01) was found. Outcome predictors were not evaluable for HB, although adverse reactions to therapy, including nephrotic syndrome, and access complications were more common among failed courses. Infection most often complicated the use of access catheters. These results are discussed within the context of the international ITT registry and upcoming prospective ITT study.

Introduction

The cumulative inhibitor incidence in severe or moderately severe haemophilia A (HA) is estimated to be as high as 33% (1). Inhibitor prevalence in haemophilia B (HB) is less frequent at 1 to 6% (2). The limited treatment options for inhibitor patients are useful in the acute management of bleeding, but less effective in providing a good long-term outcome. Consequently, morbidity and mortality associated with the haemorrhagic complications of haemophilia remain high, if not clearly defined (3).

Inhibitor eradication with immune tolerance therapy (ITT) is currently the best long-term treatment option, particularly for high titre antibodies. Since the first observation of its efficacy in HA by Professor Brackmann (4), small groups of patients have been treated with multiple high and low dose factor regimens, with and without concomitant immune modulation therapy (5-16). Success rates in the permanent eradication of inhibitor have been reported at between 62 and 90% (5-16). Despite similar overall success, time to induction of immune tolerance has differed among regimens (5-16). Previous experience with ITT in HB has been limited to a few reported patients (5, 14, 17).

Because of the intensity, long-term expense, and associated complications of the ITT performed in predominantly paediatric populations, it is important to optimize therapy. To this end, an understanding of current ITT practices, outcomes, and outcome predictors is essential. The initial and follow up reports from the International Immune Tolerance Registry (ITR) provided the first such aggregate data for HA (18-20). The ITR ultimately identified successful outcome predictors including dosage regimens of ≥ 200 units/kg/day and pre-ITT inhibitor titers ≤ 10 Bethesda Units (BU). Trends toward a higher success rate were also noted with younger age, lower pre ITT historical peak titers, as well as with inhibitor diagnosis to ITT initiation intervals of ≤ 5 years.

The North American Immune Tolerance Registry (NAITR) was initiated in 1992 as a project of the ISTH FVIII/IX Subcommittee with the goal of further understanding immune tolerance practices in Canada and the United States with respect to the identification of 1) therapeutic regimens in use; 2) therapeutic outcomes; 3) potential predictors of successful outcome and 4) complications of therapy. We now report the data collected between March 1993 and December 1999.

Methods and Materials

Data Collection

In March 1993, 168 hemophilia treatment centers in the US and Canada were invited to participate in the NAITR by completing 1) a summary form describing the hemophilia population followed at their center, and 2) a set of data collection forms on each hemophilia patient who had completed or was undergoing ITT. Data collection and updates continued through December 1999.
**Definition of Variables**

Inhibitor titres were expressed in Bethesda Units (BU). High responders (HR) were defined by a historical peak inhibitor titre prior to ITT of ≥ 5 BU. The peak historical inhibitor titre was defined as the highest recorded Bethesda titre prior to the initiation of ITT, and distinguished from the peak anamnestic response demonstrated by the patient while on ITT. The pre-ITT induction titre identified the last measurement recorded prior to the initiation of ITT. This included titres achieved by both a spontaneous decrease in antibody in the absence of re-exposure to FVIII, as well as by therapeutic intervention with immunoadsorption or plasmapheresis.

The dosing regimen for ITT included continuous delivery, single and multiple daily infusions, as well as alternate day and weekly therapy. We calculated the daily dose in units/kg of body weight by dividing the total weekly dose of clotting factor by 7 days. Daily dosing regimens were thus defined: 1) ≥ 200 units/kg/day; 2) 100-199 units/kg/day; 3) 50-99 units/kg/day; and 4) < 50 units/kg/day.

Immune modulation described any concomitant ancillary treatment used for ITT and included 1) immunoadsorption; 2) plasmapheresis; 3) immunosuppressive drugs such as cyclophosphamide, immuran, and cyclosporine A; 4) intravenous immunoglobulin; and 5) corticosteroids.

Factor VIII (FVIII) or Factor IX (FIX) concentrates in use at the time of inhibitor development and those administered for ITT were classified as follows: 1) intermediate purity (IP), defined as a specific activity (SA) 1-10 units/mg protein for FVIII and an SA < 50 for FIX; 2) high purity (HP), defined as an SA 1-100 units/mg protein for FVIII and an SA >160 for FIX; 3) monoclonal, or 4) recombinant.

ITT outcome was categorized by the individual treating physician as a success, a failure, or indeterminate because of ongoing therapy. The different criteria, as chosen by the contributing physicians to define success and failure, were recorded.

Complications during the course of treatment were categorized as either adverse events associated directly with the therapeutic regimen or events related to repeated venous access.

**Statistical Analysis of Data**

Chi-square tests of significance were used to compare the categorical outcome predictors between the treatment success and failure groups. Mean values for continuous variables were compared using student's t-test. Standard actuarial methods were used to quantify the rates of predictive markers and success. Rates of success were compared with the log-rank test.

**Results**

**Inhibitor and ITT Demographics**

A total of 68 centers (40%), submitted data to the NAITR. This represented 5,000 (43%) of the estimated individuals with HA and 1,325 (39%) of those estimated with HB in North America (21, 22). Of these, 2,489 had severe HA and 473 had severe HB. This cohort represented 43% and 35%, respectively, of the estimated severe cases in the USA and Canada.

A past or current history of an inhibitor was reported in 486 (9.7%) of HA patients and 32 (2.4%) of HB patients, including 444 (17.8%) and 30 (6.3%), respectively, of those with severe disease. Importantly, 91% of the FVIII inhibitors and 94% of FIX inhibitors occurred in patients with severe disease. High responders comprised 326 (67%) of the patients with HA and 19 (59%) of those with HB.

Among the 518 inhibitor patients at the participating centers, 188 (36%) had undergone or were still undergoing ITT at the time of the last data collection, including 171 with HA and 17 with HB. The majority (79%) of ITT courses were initiated during or after 1990. Table 1 describes the demographics of the subjects who completed ITT.

**Therapeutic Regimens**

Among the 171 HA ITT patients, 47% developed inhibitors on very high purity products (monoclonal and recombinant). However, 75% received monoclonal or recombinant FVIII for tolerisation. Among the 17 HB ITT patients, 47% of inhibitor development occurred on high purity or monoclonal FIX concentrate while 82% received these concentrates during ITT.

With respect to dosing regimen, data were available for 164/171 of the completed and ongoing ITT courses in HA patients. Fifty-two percent of subjects received doses of ≥ 100 units FVIII/kg/day. Only 14% of this cohort received ≥ 200 units/kg/day. Alternate day dosing regimens (representing the majority (91%) of the < 50 units/kg /day group), were used in 21% of completed and ongoing ITT in HA subjects. Adjunctive immune modulation (IM) therapy was used in 65 (40%) of all completed and ongoing ITT in HA patients. IM was added to 58% of FVIII dosing regimens using ≥ 100 units/kg/day and to 22% of regimens using < 100 u/kg/day. Only 4 subjects received the complete...
or modified Malmo regimen, including immunoadsorption or plasmapheresis, as a part of their tolerance protocol.

Among the 17 reported courses of ITT in HB patients, the median daily dose of FIX was 100 u/kg/day with a range of 25 to 200 units/kg/day. Daily dosing regimens were or are being used in 15 (88%) courses. Immune modulation was added to 8 (47%) and plasmapheresis was used in 2 courses.

Duration of Therapy

Hemophilia A patients who completed ITT were treated for a mean of 16.8 months (range 0 to 89) compared to those with HB who were treated for 11.6 months (p = 0.05).

Outcome Data

Of the 164 registry subjects with HA who completed ITT, 115 (70%) successfully achieved tolerance. Among HR HA patients, 81/128 (63%) were successfully tolerised. Of the 16 completed ITT courses in individuals with HB, only 5 (31%) were successful. The success rate remained constant throughout the ten-year study period.

The definition of success for both HA and HB included a negative inhibitor titre (≤ 1 BU) in 104 (87%) cases; normal FVIII recovery (≥ 70% of predicted) in 69 (56%) cases; normal factor survival (≥ 12 h) in 34 (28%) cases; and conversion from high to low responder status in 12 (10%) patients. Only 30 (25%) of the patients were determined to be successfully tolerised on the basis of a negative inhibitor titre, as well as a normal factor recovery and survival.

The most common reasons for the 60 ITT failures were 1) a late rise in inhibitor titre after an initial decline while on ITT; 2) patient/family desire to terminate ITT; and 3) central venous access device complications. Other reasons cited included adverse reaction to therapy, ineffectiveness of therapy, loss of medical insurance, patient relocation, death from unrelated causes, poor patient compliance, and enrollment in a bypassing agent study.

Outcome Predictors/Haemophilia A

Several parameters were examined as possible ITT outcome predictors in HR HA patients (Table 2). Although trends toward both a younger mean age and a shorter mean interval between inhibitor diagnosis and ITT initiation were noted in the successful group (9.5 years; 55 months) when compared to those who failed tolerance (10.6 years; 65 months), those differences were not statistically significant in this data set (p = 0.6 and 0.4 respectively). Success was predicted with only borderline significance by an interval between diagnosis and therapy of ≤ 5 years for both HA (p = 0.08) and HR HA (p = 0.17). Positive HIV serology (19% vs. 20%) and mean duration of ITT (15.6 vs. 18.8 months) were also not statistically different between the success and failure groups.

The rate of successful immune tolerance induction in a small cohort of African-Americans and Latinos with HA was similar to a larger group of patients of other races [14/21 (67%) and 11/19 (58%) vs. 99/139 (71%), p = 0.67 and 0.3 respectively].

FVIII product purity had no impact on ITT success in HA patients. The success rate among those patients tolerised with intermediate or high purity products was 67.5% and not statistically different from either that in patients tolerised with monoclonal or recombinant factor (71%), or the overall success rate in the HA population as a whole (70%).

Other potentially significant parameters examined included the interval between the last exposure to human or porcine FVIII and ITT induction; the frequency of adverse events on therapy; and the frequency of central access complications during tolerance induction. None were significant outcome predictors in this registry.

We examined the influence of inhibitor titre on ITT outcome in HR HA patients, specifically the historical peak titre prior to ITT, the peak inhibitor titre on immune tolerance and the pre ITT induction titre. All three parameters were found to be significant predictors of outcome in univariate analyses (Table 2). However, in a multivariate analysis, both the peak titre on ITT (p = 0.005) and the pre-induction titre (p = 0.001) were the most significant predictors of success. Specifically, when the pre ITT titre was < 10 BU, the ITT success rate was 83% compared to 40% when the titre was ≥ 10 BU (p = 0.001). Furthermore, when the pre ITT titre was < 10 BU, the mean time to successful tolerance was significantly shorter (14.4 months), compared to 21.7 months when ITT was begun at titres ≥ 10 BU (p = 0.02). Of note, among 22 HR HA patients with pre ITT titres of < 2 BU, all achieved ITT success within a mean treatment time of 7.1 months.

The impact of dosing regimen on ITT success in the HR HA cohort demonstrated no trend toward higher ITT success rates with increasing daily doses of FVIII. Conversely, there was a significant inverse association between total daily dose (units/kg/day) and success: (72% in the < 50 group; 65% in the 50-99 group; 68% in the 100-199 cohort; and 38% in the ≥ 200 group, p = 0.014). The use of adjunctive immune modulation had no impact on the rate of successful ITT within each dose category (data not shown). Furthermore, when the time to successful ITT was examined, there was no statistically significant difference among the dosing categories, with or without immune modulation. However, in HR HA individuals who received at least 50 units/kg/day,
tolerance was achieved significantly faster (mean of 15.9 months) when compared with those who infused with less than 50 units/kg/day (mean of 23.6 months) (p = 0.04).

Outcome Predictors/Haemophilia B

Potentially important outcome parameters are described in Table 3 for the 16 completed ITT courses administered to inhibitor patients with HB. Because of the small numbers of patients, only trends could be observed in variables such as pre-induction and historical peak titres, both of which were statistically significant predictors of success in HA. Of note, 5/11 failures had a positive family history of an inhibitor compared to none of the 5 successful outcomes. Furthermore, many of the failed patients had access complications (9/11) and adverse reactions (8/11) compared to few such events among the successes.

Adverse Reactions on ITT

Haemophilia A

Among the 171 completed and ongoing ITT subjects, 10 (6%) therapeutic courses were complicated by 14 adverse reactions to treatment. Allergic reactions accounted for 6 (4.3%) events and included 4 with respiratory symptoms and 2 episodes of cardiovascular collapse. The other adverse events included 3 episodes of bleeding and 1 of each of DIC, hair loss, gastrointestinal toxicity, headache and hypertension. With respect to viral transmission, one seroconversion to HIV and no seroconversions to hepatitis A, B or C was reported. An analysis of adverse event frequency relative to ITT dose was possible for 159 HA subjects. Of note, none of the 33 individuals receiving < 50 u/kg/day (mostly alternate day regimens) experienced adverse reactions to therapy compared to 8/126 subjects receiving ≥ 50 u/kg/day (mostly daily regimens) (p = 0.14).

Haemophilia B

Among the 17 completed and ongoing ITT courses, 14 adverse events were reported in 10 subjects undergoing 11 (65%) courses of ITT, a frequency ten times higher than that for individuals with HA. Allergic reactions accounted for 11 (79%) adverse events and occurred in the 10 subjects who had previously exhibited allergic reactions to FIX replacement therapy subsequent to the development of an inhibitor. Three of these reactions were severe and caused premature cessation of ITT. Overall, allergic reactions represented the major reason for failure in 5/11 unsuccessful courses of ITT in HB.

The registry noted an unexpected and important association between allergic reactions to FIX and the development of nephrotic syndrome in 3 HB patients undergoing ITT. In all 3 subjects, symptoms of periobital edema, proteinuria and hypoalbuminemia developed 7 to 9 months into ITT. All received 100 units/kg/day of either prothrombin complex concentrate or monoclonal FIX, and had exhibited a decline in inhibitor titre prior to the diagnosis of nephrosis. There were no reported viral seroconversions. When adverse reactions were examined relative to dose, adverse events were not noted to occur any less frequently with doses < 50 u/kg/day (4/4) compared to daily doses of ≥ 50 u/kg/day (7/13) (p = .09).

Central Venous Access Catheter Complications

There were 129 access complications reported with the use of 136 central access devices (CAD), including both external catheters and venous ports inserted for ITT. Thirteen complications were reported among 18 indwelling peripheral intravenous catheters. Infections accounted for ≥ 60% of the complications occurring in each type of catheter. The 79 CAD infections led to 55 hospitalizations and necessitated catheter removal in 18 cases. CAD-associated bleeding was the second most common complication (18/129, 14%), with packed red

### Table 3 Characterization of HB patients who completed immune tolerance therapy (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Success (N = 5)</th>
<th>Failure (N = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIX activity &lt; 1%:</td>
<td>5/5</td>
<td>11/11</td>
</tr>
<tr>
<td>Family history inhibitor:</td>
<td>0/5</td>
<td>5/11</td>
</tr>
<tr>
<td>African-American race:</td>
<td>2/5</td>
<td>2/11</td>
</tr>
<tr>
<td>Age at ITT induction (years) *</td>
<td>3.7 (2.4 - 4.8)</td>
<td>4.6 (0.8 - 19.6)</td>
</tr>
<tr>
<td>Interval between diagnosis / ITT (months) *</td>
<td>12 (0 - 31)</td>
<td>47 (0 - 227)</td>
</tr>
<tr>
<td>Duration of ITT (months) *</td>
<td>12 (5 - 18)</td>
<td>7 (2 - 32)</td>
</tr>
<tr>
<td>High responder (≥ 5 BU)</td>
<td>4/5</td>
<td>9/11</td>
</tr>
<tr>
<td>Historical peak titre (BU)*</td>
<td>13 (2.4 - 112)</td>
<td>50 (10 - 650)</td>
</tr>
<tr>
<td>Pre-Induction titre (BU)*</td>
<td>5 (3 - 24)</td>
<td>10.5 (1 - 19)</td>
</tr>
<tr>
<td>Peak titre on ITT (BU)*</td>
<td>20 (3 - 38)</td>
<td>39.5 (6 - 59)</td>
</tr>
<tr>
<td>ITT dose (units/kg/day)*</td>
<td>100 (43 - 200)</td>
<td>75 (25 - 200)</td>
</tr>
<tr>
<td>Access complications</td>
<td>0/5</td>
<td>9/11</td>
</tr>
<tr>
<td>Adverse reactions</td>
<td>2/5</td>
<td>8/11</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>1/5</td>
<td>4/11</td>
</tr>
</tbody>
</table>

* Results reported as median (range). ITT = immune tolerance therapy. BU = Bethesda units
cell transfusions required in two episodes. However, among external CAD, accidental loss was reported as the second most common complication (14/88 events, 16%). CAD-associated thrombosis necessitated the removal of the access device in 5/9 (56%) events. As might be expected, access complications in subjects with HA and HB were significantly less frequent in these subjects receiving < 50 u/kg/day or primarily alternate day regimens (5/37), when compared to largely daily regimens of ≥ 50 u/kg/day (62/140) (p = .0006).

Discussion

The North American Immune Tolerance Registry represents the second retrospective characterisation of a large cohort of HA inhibitor patients who completed ITT. It was performed in an effort to further understand both outcome and outcome predictors relevant to the ITT practices within North America. The study differs from its predecessor, the International Immune Tolerance Registry previously reported by Mariani et al. in 1994 (18) in that 1) haemophilia B inhibitor patients were included; 2) potential outcome predictors such as race and peak inhibitor titre on ITT were also studied; and 3) complications secondary to clotting factor administration as well as frequent venous access were recorded.

A recent comparison by Kroner of the haemophilia A cohorts in both registries, revealed that the IITR and NAITR study groups were similar in number of subjects studied (249 vs. 177, now 188) as well as in the prevalence of HIV seronegativity (81% vs. 84%). The two registries were also similar with respect to the following therapeutic parameters: mean interval months between inhibitor diagnosis and the initiation of ITT (51 vs. 54); the mean / median inhibitor titres just prior to the start of ITT (48/7 vs. 30/6 BU); and the percent of patients who received at least 100 units/kg/day of FVIII as part of that tolerance regimen (48% vs. 52%) respectively (20).

However, the HA IITR and NAITR cohorts differed in the mean ages of the patients at inhibitor diagnosis and ITT initiation (10 and 15 vs. 9 and 4 years respectively); the mean/median historical peak titres prior to ITT (624 and 64 vs. 286 and 35 BU respectively); the percent of the cohort that both underwent tolerance prior to 1990 (66% vs. 21%) and thus received intermediate purity FVIII (95% vs. 20%); as well as the mean duration of ITT (18 vs. 12.6 months). Although a trend toward increased daily doses was observed in the ongoing ITT cohort within the NAITR, fewer patients received FVIII doses of ≥ 200 u/kg/day when compared to the IITR (13% vs. 31%). Also, although the IITR uniformly defined tolerance by a normalized FVIII recovery and survival, only 30% of the successful ITT was so defined in the NAITR (20).

Within the context of the similarities and differences in the two registries cohorts, outcome and outcome predictors are compared. When the definition of success includes conversion from high to low responder, overall successful outcome was similar in both registries (67% vs. 77%). Among the significant outcome predictors, a pre ITT inhibitor titre < 10 BU was highly predictive of success in both the NAITR (p = .004) and the IITR analyses (p = .004–0.07) (18, 19). The inverse correlation between historical peak titre and success identified by the NAITR was corroborated by a further analysis of the international data (p = .002 by univariate and p = .06 by multivariate analyses) (19). Finally, product purity was evaluated in both registries and not found to be significant in either. However, both analyses were confounded by the predominant use of one type of product: intermediate purity in the IITR and ultra high purity product in the NAITR (20).

Conversely, both age at initiation of ITT and higher daily doses of FVIII were both strong predictors of success in the IITR, but not in the NAITR (19, 20). Its significantly younger cohort may have diminished the importance of age in the NAITR when compared to the IITR. With respect to dosing, the latest analysis of the IITR by Mariani and Kroner, suggested that the advantage of higher daily dosing was most significant for individuals receiving at least 200 u/kg of FVIII per day. Although 31% of the IITR cohort received such doses, only 13% of the subjects in the NAITR were comparably treated. Therefore, this high dose advantage may not have been fully appreciated in this study. Importantly, although a direct correlation between dose and success was not corroborated by the NAITR, daily dosing regimens of at least 50 units/kg/day did shorten the time to successful tolerance. Consequently, optimal FVIII dosing undoubtedly remains the most disputed therapeutic strategy in the practice of ITT.

Two variables with potential impact on the success of ITT were exclusively addressed by the NAITR. The first was the impact of peak inhibitor titre achieved during ITT on therapeutic success. In high responders, the inverse correlation between peak titre and successful outcome was as significant as pre-induction titre. Therefore, this variable should be further studied in any future prospective study of ITT outcome parameters. The second examined was the patient’s racial background. The higher incidence of inhibitors in African Americans has been previously reported (23, 24). However, in the study of a small cohort of patients, the NAITR did not demonstrate a significant difference in the African American response to ITT when compared to people of other races. The ongoing study of this group of patients will be required to document any potential discrepancy in successful outcome and, if necessary, develop new strategies to improve ITT outcome in this inhibitor-susceptible population.

Although the HB cohort of 17 ITT patients characterised by the NAITR is small, it represents the largest group of these patients reported to date. Successful tolerance in HB was much less frequent than in HA. Because of the few completed courses of therapy available for analyses, only trends were observed in the significant outcome parameters identified for HA. However, in contrast to the HA patients, adverse reactions and venous access device complications were common in HB patients who failed tolerance. The more frequent adverse reactions were of particular interest since the majority occurred in FIX patients who previously exhibited allergic symptoms coincident with inhibitor development (25, 26). Severe allergic reactions to FIX ITT regimens accounted for 79% of the adverse reactions reported. Furthermore, the occurrence of nephrotic syndrome, a previously unknown serious complication of high dose ITT in the allergic FIX inhibitor patient was first identified by the NAITR and reported by Ewenstein et al. (27). Together, intolerable allergic reactions and the development of nephrotic syndrome represented the major reasons for failure in the HB cohort. Given the frequency of these complications as well as a high rate of ITT failure, immune tolerance should currently be undertaken with extreme caution, if at all, in the FIX inhibitor patient with an allergic diathesis.

In summary, the NAITR accomplished its goal in characterising ITT practices, outcomes, outcome predictors and complications in a large North American population of HA and HB inhibitor patients. However, in that it was a retrospective data gathering tool, the registry was limited in its capacity to provide definitive answers to the many unresolved issues surrounding the practice of immune tolerance. Nonetheless, the data generated has helped to formulate the hypotheses to be tested in the logical next step – the international randomized prospective study of immune tolerance.
Acknowledgements

The authors wish to acknowledge Dr. Carol Kasper for her role in stimulating this study and Ms. Valisha McFarlane for her invaluable assistance in the preparation of this manuscript. We also wish to thank Drs. William Hathaway, Louis Aledort, Margaret Hilgartner as well as the ISTH FVIII/IX Subcommittee members for their valuable comments. Data analysis was supported by a grant from the Hemophilia Research Society of North America (HRS-1001).

Dedication

This manuscript is dedicated to the late Dr. T. John Gribble for his contributions to this registry and his lifelong devotion to hemophilia patients with inhibitors.

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21. Data supplied by the National Hemophilia Foundation (US).
22. Data supplied by the Canadian Hemophilia Society.

Received July 9, 2001 Accepted after revision September 27, 2001