Granulocyte, Monocyte Apheresis Treatment in Pediatric Inflammatory Bowel Disease

Selective leukocyte apheresis is a new type of non-pharmacological treatment of inflammatory bowel disease. As an increased number of activated granulocytes and monocytes/macrophages have an important role in relapses of inflammatory bowel diseases, removal of this excess is believed to attenuate the inflammatory process. Data on adult patients have shown this treatment to be efficacious and safe. Although studies in pediatric patients remain scanty, preliminary results are promising and encouraging to future research in the treatment of pediatric ulcerative colitis and Crohn’s disease. This task is demanding and new treatment options are urgently needed.

The number of young patients with inflammatory bowel disease (IBD)—comprising Crohn’s disease (CD) and ulcerative colitis (UC)—is increasing markedly in Western countries; during the last twenty years the incidence of patients has doubled in Scandinavia (1,2). Treatment of chronic bowel diseases in childhood and youth is especially demanding in that it involves patients whose growth and psychosocial development is an ongoing process (3). The mainstay in the treatment of IBD is to ensure the normal growth, reproductive health, education and psychosocial well-being of the child.

The usual treatment of IBD consists of 5-ASA or sulphasalazine as basic treatment; most patients, however, need additional treatments with corticosteroids and other immunosuppressants such as azathioprine, 6-mercaptopurine, or methotrexate and biologic treat-
ments. In Crohn’s disease exclusive enteral treatment is a viable option in many patients (4) but has not proved effective in UC. Regardless of other treatments, almost half of IBD children are corticosteroid-dependent (5). Although the initial response to infliximab in Crohn’s disease can be as good as 94%, the majority of patients, 66%, remain dependent on maintenance therapy (6,7). Surgery is the final option being necessary in 1/3 of Crohn’s patients and in 24% of UC patients (8).

Side-effects are common: it is known that long-term corticosteroid treatment can cause growth failure (9), impaired bone density (10), altered fat deposit, lowered sugar tolerance and dermatological problems. Immunomodulators can affect the liver, kidneys and bone-marrow and with prolonged use carry a possible risk of lymphomas. An increased number of infections such as abscesses, septicemia and tuberculosis has been noted in patients using biological treatments (11) and hepatosplenic T-cell lymphomas have more recently been reported in connection with their use (12). Although the most severe side-effects are rare, they must be carefully considered when treating children. Side-effects are also rather common after surgery, being seen in 31–36% of cases both shortly after surgery but also in 10 years follow-up. As many as 75% of patients has at least one side-effect and 54% undergo a reoperation (13). Very little is known to date regarding fertility in adulthood after UC surgery in childhood. Studies among operated women show female fecundity to be clearly reduced after UC surgery (14). Although UC itself does not affect fertility, pediatricians should keep this in mind when considering and timing an operation. New treatment options are thus clearly called for especially for children.

Granulocyte, monocyte apheresis has been used as a new therapeutic method for the treatment of chronic inflammatory bowel disease. In IBD circulating activated granulocytes and macrophages/ monocytes are increased to approximately twice the concentrations seen in healthy individuals; in patients with severely active disease, the granulocyte concentrations are about 3 times higher. These cells also have a prolonged life—span and infiltrate the bowel, causing tissue injury by producing inflammatory cytokines, which are involved in the initiation and perpetuation of an inflammatory disorder (15,16,17,18). Periodic removal of activated granulocytes and monocytes/ macrophages is assumed to reduce leukocyte-dependent tissue injury. Despite their removal, however, the number of these cells does not fall below the normal range in the peripheral blood as an influx of new granulocytes into the circulation has been observed. These new cells in the circulation are inactivated and immature and therefore not inflammatory (19).

Apheresis is a method of extracorporeal removing cells from the circulatory system. The use of columns to remove specific components from whole blood has proved to attain more active modification of cellular immunity than simple centrifugation. Selective apheresis has been evaluated as a treatment of several autoimmune diseases including rheumatoid arthritis and IBD (20,21). At present two different apheresis systems are available: Cellsorba (Asahi Medical, Tokyo, Japan) which uses polyester fibers, the filter removing granulocytes, monocytes, lymphocytes and some platelets. The second method is Adacolumn (JIMRO, Takasaki, Japan), which has a column of cellulose acetate beads. With Adacolumn, about 65% of granulocytes and 55% of monocytes are adsorbed while there is no significant change in the number of lymphocytes or platelets. Most of the published apheresis studies have used this latter system.

**ADACOLUMN TECHNIQUE**

GMA is used in children according to the same principles as in adults. Adacolumn columns are of 335 ml capacity filled with 220 g of cellulose diacetate beads 2 mm in diameter. The column is placed in an extracorporeal setting. Blood from one antecubital vein is flowed into the column at 30 ml/min and returned to the patient via the antecubital vein on the other arm; one treatment session lasts 60 min. Eighteen-gauge cannules are best for cannulation to ensure sufficient circulation. If children are anxious before the first treatment, this being mild sedative can be given orally (midazolam, diazepam), this also being helpful in preventing venous spasms. Furthermore, if the child is dehydrated, Ringer solution can be given 10–20 ml/kg before initiation of the treatment. We have noted that this procedure improves the circulation and renders the GMA technically easier to conduct.
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No minimum age for GMA is given, but the manufacturer had recommended a minimum weight of 30 kg.

**CLINICAL EXPERIENCE ON GMA**

Most published studies report concern adult patients. In a large Scandinavian study (22) of 100 adult patients with IBD, 52 patients with UC, 44 with Crohn’s disease and 4 with indeterminate colitis, were treated with GMA; 97% were either corticosteroid-dependent or corticosteroid-refractory. Clinical remission (defined as an absence/near absence of symptoms) was attained in 48% of UC patients and in addition 27% evinced clinical response (improvement of symptoms) to GMA treatment. In the Crohn’s group 41% attained remission and 23% gave partial response. Tomomasa and coworkers (23) evaluated retrospectively 12 children with UC, mean age 12.2 years; they received GMA treatment for 5–10 consecutive weeks. In 8 patients clinical symptoms were alleviated after two GMA sessions. The steroid dose was tapered during GMA therapy by 50%. No serious adverse effects were noted. Four out of the 8 cases relapsed 3.5 (SD 2.2) months after the last GMA session, while the other 4 were in remission up to 22.8 (SD 18.1) months. A study by de Carpi et al (24) and associates involved 5 children with UC and 4 with Crohn’s disease; mean age 13 years 9 months and mean disease duration was 28 months. All UC patients were steroid-dependent and Crohn’s patients had been treated unsuccessfully with other therapies, including enteral nutrition, steroids, immunomodulators and biologics. After 5 GMA sessions 4 out of 5 UC patients and 1 of the 4 Crohn’s patients achieved remission and steroids could be tapered off in 3 out of 5. After a one year follow-up, 2 out of 4 UC patients were still in remission as was also the one Crohn’s patient. The treatment proved to be safe and well tolerated.

In Scandinavia GMA treatment has been used for IBD in pediatric patients, and our data have been collected from 3 countries: Denmark, Sweden and Finland (25). We had altogether 37 patients, 22 with UC and 13 with Crohn’s disease and two with indeterminate colitis. The indication for GMA treatment was steroid dependency in 54% of cases. Twenty-four per cent were steroid-resistant. The rest (22%) either had side-effects from other treatments, refused conventional treatments, had poor growth or were hoped to achieve a better clinical condition before surgery (one child). All patients had moderate-to-severe disease, 95% used 5-ASA/sulphasalazine, 84% azathioprine/methotrexate, and 81% were on steroids.

Apheresis treatment was given once a week for 5 to 10 sessions. Patients were evaluated at the beginning, at the end and three months after the end of GMA treatment. Treatment response was evaluated in 3 different ways: 1. using the severity index PUCAI for UC and PCDAI for Crohn’s disease, 2. tapering of corticosteroids and 3. clinical response at the end of treatment. Clinical response was rated complete if the patient had <3 stools/day, there was no blood in the stools and the child had no abdominal pain and pursued normal social activity. Response was partial when there was regression in symptoms, the number of stools was <5/d and blood was seen occasionally but not daily. No response was defined when the patient showed no benefit from the treatment.

In the UC group, the mean PUCAI points before treatment were 38.8 (SD 21.8), at the end of treatment 10.1 (SD 5) (p = 0.001) and three months later 4.6 (SD 6.2) (p = 0.002). Corticosteroids were tapered off altogether only in 4/19 UC children during the follow-up while a significant reduction of the corticosteroid dose was seen, from 22.5 mg at the beginning to 15 mg after the treatment and to 7.5 mg 3 months later in the remainder.

In the Crohn’s group, the mean PCDAI before treatment was 31.1 (SD 23.7), at the end of treatment 23.2 (SD 23.5) (p = NS) and three months later 8.2 (SD 8.1) (p = 0.025). The two children with IC had a baseline mean PUCAI index of 50(SD 0), at the end 5 (SD 0), and three months later 37.5 (SD10.6). Corticosteroid dosages were 12.5 mg-15 mg-5 mg in Crohn’s patients at the beginning, at the end and three months after treatment.

The clinical response data are shown in Table 1. Treatment was well tolerated. Thirty percent of the children had a headache after the treatment, this resolving with one dose of paracetamol. Most complained of tiredness the day after the apheresis. This, however, had no effect on daily activities such as...
school attendance. None of the children considered the treatment unpleasant or wished to discontinue. One child had more than usual bleeding after the first two apheresis sessions, this could possibly be due to routinely given heparin during the treatment or to deterioration of the UC. Her clinical condition subsequently improved rapidly.

Relapses were seen during the follow-up in 14% in the UC group and 23% in the CD group.

CONCLUSION

In the retrospective analysis of GMA treatment in pediatric IBD patients, GMA showed good response especially in the treatment of corticosteroid-dependent and corticosteroid-resistant UC patients. Treatment was also well tolerated and side-effects were mild.

As the cohort was particularly heterogeneous, we cannot draw conclusions from any sub-groups. Most of the patients were corticosteroid-dependent, these being our most problematic group of patients to treat and subject to various side-effects. The number of relapses after treatment was comparable to rates seen with other treatments and is attributable to the chronic relapsing nature of these diseases. The question of maintenance therapy with GMA in pediatric IBD must thus be considered.

For the treatment procedure, it is advisable to have a well-trained pediatric nurse to perform it and skilled doctor to insert the needle. When surroundings and staff are understanding and reliable, the child relaxes and treatment goes smoothly.

The cost of new treatment seems nowadays always to be too high. There is so far only one paper evaluating the cost-effectiveness of GMA treatment (26). The cost of traditional treatment and GMA were compared, the conclusion being that GMA in the therapeutic management of moderate-to-severe UC patients is cost-effective and ensures savings related to a reduction in the adverse effects of corticosteroids and to the decreased number of surgical interventions required.

Further research is needed to evaluate which patients will benefit from this treatment and what will the optimal number of treatment sessions as well as of maintenance therapy.

Table 1. Clinical response to the leukocyte apheresis treatment

<table>
<thead>
<tr>
<th></th>
<th>Complete response</th>
<th>Partial response</th>
<th>No response</th>
<th>p*</th>
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</thead>
<tbody>
<tr>
<td>CD</td>
<td>3 (23%)</td>
<td>7 (54%)</td>
<td>3 (23%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UC</td>
<td>16 (72%)</td>
<td>3 (14%)</td>
<td>3 (14%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All</td>
<td>20 (54%)</td>
<td>10 (27%)</td>
<td>7 (19%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Pearson chi square test

References

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