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Intramuscular immunoglobulin for recalcitrant suppurative diseases of the skin: a retrospective review of 63 cases

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Conflicts of interest
None declared.

Summary

Background Intramuscular human immunoglobulin (HIG) may provide a therapeutic option as an independent or combined treatment for recalcitrant suppurative skin diseases such as hidradenitis suppurativa, folliculitis decalvans, or chronic recurrent furunculosis or folliculitis.

Objectives To define the efficacy and safety of intramuscular HIG for chronic and recalcitrant suppurative skin diseases.

Methods Patients who had received HIG for hidradenitis suppurativa, folliculitis decalvans, furunculosis or folliculitis at Severance Hospital, Seoul, Korea, between January 2000 and May 2005 were identified from medical/pharmacy records. All records were analysed retrospectively.

Results Sixty-three patients were identified. After treatment, 37 patients (59%) showed overall improvement and were rated as having an 'excellent response' or 'good response' by the attending physician. No improvement or worsening was seen in only three patients (5%). A period without new lesions (PWNL) was achieved in 46 patients (73%). The number of times HIG was administered to achieve PWNL ranged from 1 to 12 (mean ± SD 2·15 ± 1·69). There was no significant difference in the rating score between the independent intramuscular HIG and the combined treatment groups. Pain at the injection site was the major side-effect, which led to the discontinuation of treatment in five patients. No other significant systemic side-effects were observed.

Conclusions Our results demonstrate that intramuscular HIG may be used for the treatment of recalcitrant suppurative skin diseases as an independent or combined treatment.

Human immunoglobulin (HIG) is widely used for numerous human diseases. Generally, HIG can be used to induce passive humoral immunity regardless of host immune status, usually in patients with immunocompromised or immunodeficient status. For skin diseases, HIG could be used in the same manner although the applicable cases are limited. Mimouni *et al.*[1] previously reported an unintended prophylactic or protective effect caused by nonspecific HIG treatments when used against diverse skin diseases including bacterial skin infections in immunocompetent persons. However, in this study, much smaller doses were administered compared with the typical systemic intravenous administration.

HIG has numerous immunomodulatory actions. This immunomodulation is primarily used to decrease inflammatory reactions by controlling various components of immune mechanisms.[2] There are more indications in which this aspect is applicable, including many dermatological diseases, in which the exact biological actions have only been partially elucidated.

Hidradenitis suppurativa, folliculitis decalvans and chronic recurrent folliculitis or furunculosis are considered pathophysiologically multifactorial.[3] Bacterial infection is thought to be a major pathophysiological and aetiological factor despite some controversies[3,4] and most patients have been treated with antibiotics as a first-line therapy with or without microbiological evidence, with varied responses. However, despite various conventional pharmacological and surgical treatments, the clinical disease course tends to become chronic and recurrent in a significant portion of cases.[5] In these cases, other pathophysiological factors such as follicular structural abnormalities[4] and endocrine[3,6–9] and immunological imbalances[10] are to be considered.

Herein we describe our observations of the efficacy of intramuscular HIG in the treatment of recurrent suppurative diseases of the skin.

Materials and methods

Study design

This is a retrospective study of an open-label, noncomparative use of intramuscularly injected HIG in the treatment of recalcitrant suppurative skin diseases. The study ran from January 2000 to May 2005 at a single centre (Severance Hospital, Seodaemun-gu, Seoul) in Korea. All of the study procedures were approved by an institutional review board at the investigational centre.

Patient selection

Adult patients with a history of chronic suppurative skin disease and multiple recurrences or continued development of new lesions despite various treatments were selected according to the following criteria: (i) cases that showed incomplete responses to initial antibiotic therapy; (ii) diseases known to be pathophysiologically multifactorial; and (iii) suppurative diseases resulting in tissue destruction and scarring. Hidradenitis suppurativa was the first indication but this was expanded after seeing favourable responses in the initial off-label trials on the other diseases mentioned above.

The following parameters were recorded: patient sex and age, clinical diagnosis, duration of the disease, concurrent diseases, disease sites, and previous medical or surgical treatment history. Baseline patient characteristics are summarized in Table 1.

Table 1 Baseline patient characteristics

Characteristic	n
Age[a]	
Range (years)	
20–29	20
30–39	17
40–49	17
50–59	5
60–69	3
≥ 70	1
Sex	
Male	36
Female	27
Site[b]	
Head and neck	
Scalp	17
Face	25
Neck	2
Trunk	
Chest	4
Axilla	2
Back	6
Abdomen	2
Buttocks	13
Groin	3
Extremities	
Thigh	4
Arm	1
Diagnosis	
Chronic recurrent folliculitis	35 (56%)
Chronic recurrent furunculosis	18 (29%)
Hidradenitis suppurativa	5 (7%)
Folliculitis decalvans	3 (5%)
Recurrent erysipelas	2 (3%)

[a]Mean ± SD age was 37·2 ± 13·3 years. [b]More than one site was affected in some patients.

Treatment

Intramuscular HIG (165 mg/2 mL per vial; Green Cross PBM, Seoul, Korea) was administered on average once a month at the upper lateral side of the gluteus muscle (0·15 mL kg^{-1} or 12·38 mg kg^{-1} in principle, modified according to the range of patient body weights: 8 mL for 40–60 kg, 10 mL for 60–80 kg, 12 mL for 80–100 kg). Administration intervals were modified according to the patient's response.

Clinical assessment and outcomes measurement

The overall improvement was assessed by one attending physician at the end of the recorded treatment sessions using descriptive/numerical rating. Before initiating the analysis, the investigators interviewed the attending physician on the rating standard of those records and agreed to interpret the ratings without any information on the distribution of the collected data. The standard is summarized in Table 2. According to this principle, we used the converted values, designated global improvement score (GIS), for statistical analysis to compare the two groups.

Table 2 Criteria used for the interpretation of the clinical improvement described in the medical records

Percentage or fractional improvement (converted to the equivalent percentage)	Description	Global improvement score
Worsened	No response or worsened	0
0–25% improvement	Poor	1
25–50% improvement	Moderate	2
50–70% improvement	Good	3
70–100% improvement	Excellent	4

The period without new lesions (PWNL) was defined as the days or weeks that were free of newly developed papules, pustules or nodules. PWNL was described by the patient and recorded at each visit. Principally, once PWNL was achieved, the treatments were suspended. If PWNL continued on the next visit, prolonged PWNL was recorded. Once recurrence or

discontinuation of PWNL was reported, monthly treatments were re-initiated.

To examine the effect of other concomitant treatments, patients were divided into two groups (group A, with other treatments; group B, without other treatments during the study period) and a comparison was made by analysing the difference between the two groups with regards to GIS and PWNL values. A safety assessment was performed by monitoring and recording all adverse events, local or systemic irritation, or other complaints from the patients.

Statistical analysis

To compare with the baseline, a one-sample t-test was used in the GIS analysis. The PWNL data were analysed by Spearman's correlation test to determine if there was a correlation between the number of times the treatment was administered and the PWNL duration. The comparison between the concomitant treatment groups was accomplished by a Wilcoxon signed rank test for equality of variances and a paired t-test for equality of means. All analyses, summaries and visualizations were performed using Sigmaplot 9.0 and SPSS version 11.5 (SPSS Inc., Chicago, IL, U.S.A.).

Results

Study population

Data from a total 63 patients were collected and analysed. The disease duration ranged from 1 month to 30 years (mean ± SD 63·92 ± 73·39 months). Although we did not exclude any patients according to their immune status, no patients had evidence of immunodeficiency or immunocompromised status in their medical histories, systemic reviews, physical examinations, or in their available initial or recent laboratory findings. Therefore all patients were considered to be immunocompetent. No patient was enrolled with a history of a known IgA deficiency. Most patients (49 of 63) had a history of various treatments, which had been either temporarily or poorly effective. Treatment history is summarized in Table 3.

Table 3 Summary of treatment history

Previous treatments[a]	n
Antibacterials[b]	18
Antifungals[c]	6
Corticosteroids	8
Dapsone	1
Sulfasalazine	1
Retinoids	6
Corticosteroid intralesional injection (triamcinolone)	8
Incision and drainage	11
Excision	6
Chemical peeling	10
Herbal medication	3
None of the above (no previous treatments)	14

[a]Patients could have received more than one type of treatment. [b]Including mupirocin (topical), tetracycline, amoxicillin, minocycline, erythromycin, metronidazole, ciprofloxacin and cephalosporins. [c]Including topical or systemic itraconazole, ketoconazole and terbinafine.

Study duration and dosage

The total number of times the treatment was administered ranged from 1 to 15 (mean ± SD 3·51 ± 2·77). The total dose administered ranged from 8 to 120 mL (mean ± SD 32·73 ± 24·21).

Efficacy

Total subjects

The overall improvement of the patients was impressive. Thirty-seven patients (59%) had an overall improvement rating of 'excellent response' or 'good response' by the attending physician. Only three patients (5%) showed no improvement or worsening of symptoms. The mean ± SD GIS was 2·52 ± 1·02, which was statistically significant ($P < 0·01$). The GIS results are summarized in Table 4.

Table 4 Final global improvement score (GIS)

GIS (final)	Grade	n	Percentage
Total (n = 63)	0	3	5
	1	9	14
	2	14	22
	3	33	52
	4	4	6
Chronic recurrent folliculitis (n = 35)	0	2	6
	1	8	23
	2	8	23
	3	16	46
	4	1	3
Chronic recurrent furunculosis (n = 18)	0	0	0
	1	1	6
	2	6	33
	3	8	44
	4	3	17
Hidradenitis suppurativa (n = 5)	0	1	20
	1	0	0
	2	0	0
	3	4	80
	4	0	0
Folliculitis decalvans (n = 3)	0	0	0
	1	0	0
	2	0	0
	3	3	100
	4	0	0
Recurrent erysipelas (n = 2)	0	0	0
	1	0	0
	2	0	0
	3	2	100
	4	0	0

PWNL was achieved in 46 patients (73%). The number of treatments administered to achieve PWNL ranged from 1 to 12 (mean ± SD 2·15 ± 1·69). The PWNL duration (months) and the number of treatments to achieve PWNL had a correlation coefficient of $r = 0{\cdot}287$ (statistically significant at $P < 0{\cdot}01$).

Individual disease groups

All disease groups showed increased GIS, while the folliculitis decalvans and recurrent erysipelas groups showed statistically nonsignificant results due to the small numbers. All individual groups showed positive but statistically insignificant correlation coefficients (ranging from 0·036 to 0·467) between the PWNL duration and the number of treatments.

Concomitant medication and patient variations

Thirteen patients had other concomitant treatments (group A) and 50 patients did not have any concomitant treatments during the study period (group B). The GIS ($P = 0{\cdot}387$) and PWNL ($P = 0{\cdot}946$) showed no statistically significant differences between the two groups. In group A, two patients received antifungal treatment due to KOH smear-positive fungal infections at other parts of the body (toenail and groin). One patient received antituberculosis agents due to an overlapping clinical finding of tuberculids, a strongly positive purified protein derivative test, and a relatively low response to HIG only. Three patients received other treatments, mainly antibiotics, from other clinics. The remaining seven patients were also classified in group A because of prescriptions received for other medical reasons that partially overlapped with the study period.

Safety

Pain at the injection site was the most frequent complaint from the patients. Most patients ($n = 33$, 52%) described various degrees of pain, which led to the discontinuation of treatment in five patients. Short-term (disappearing within a few days) erythema was the second most common side-effect ($n = 5$, 8%). Three patients complained of hyperpigmentation at the injection site, but this was not distinguishable from the adjacent skin lesions. No other significant systemic side-effects such as shock, anaphylaxis, renal failure or cardiovascular accidents were reported.

Discussion

The present study shows that repeated administration of nonspecific HIG significantly reduced the severity and development of new lesions in recalcitrant suppurative diseases of the skin. HIG is supplied as a commercial product from pooled human serum from multiple donors. This product contains of all the existing HIG subclasses (IgM, IgD, IgE, IgA and IgG), but primarily comprises the IgG class. HIG is distributed between intravascular and extravascular spaces and has a half-life of between 3 and 5 weeks,[11–13] a factor that was the basis of our monthly administration schedule.

Intramuscular administration is not a common way to administer HIG in the field of dermatology. However, intramuscular HIG in this study showed some advantages. The amount given monthly, 8–12 mL, is much less than the dosage used in 'high-dose' HIG treatment regimens[14] and the drug costs are much lower. This gap could be even wider when considering the additional cost required for hospital admission.[15] In most cases, the cost was also much lower than that of the conventional treatments previously received by the patients. A relatively long follow-up interval was another advantage and most patients were satisfied with the effect of the treatment as a maintenance therapy. Intramuscular injection is a procedure performed in the hospital, and compliance was satisfactory in most cases. On the other hand, some adverse effects arose and required the close attention of both the physician and the patients. The most common side-effect was pain at the injection site: this was presumed to result from tissue expansion owing to the relatively large volume of the drug that was administered. Localized erythema that lasted for a few days might be caused by other mechanisms, such as allergic reaction or irritation by additives such as polyethylene glycol or thimerosal. The more severe adverse effects that have been previously reported with high-dose intravascular administration (e.g. shock, anaphylaxis, deep vein thrombosis or disseminated intravascular coagulation[12,14–18]) were not observed in our study.

On the issue of possible transmission of infectious organisms, the clinical safety of HIG is generally accepted. Licensed manufacturers are required to have an officially certified strategy and system to minimize the possibility of transmission, mostly focused on preventing viral transmission.[17] Many reports suggest the possibility of transmitting viruses including hepatitis B and C viruses, human immunodeficiency virus and human parvovirus B19. However, those findings have mostly been from studies in immunodeficient or immunocompromised patients.[17,19–21] Information is lacking on the immunocompetent population in which the possibility of transmission could be considered lower. Nevertheless, physicians should pay attention to the possibility of unidentified pathogens and should inform patients of this fact.

Although this study was not intended to define the drug mechanism of action, we can make some speculations from the study data and other literature. We postulate two main possible mechanisms. The first possibility is that the chronic, recurrent nature of the diseases partially resulted from an unidentified alteration of cutaneous immunity to the pathogens. Some immune cell dysfunction was previously reported in patients with chronic, recurrent furunculosis and hidradenitis suppurativa.[3,10,17,22–26] These patients showed a decrease in neutrophil functions, phagocytotic activities, and alteration of the ratio of B-cell and suppressor T-cell counts. As HIG induces humoral immunity, HIG treatment could be helpful in reversing these abnormalities. Secondly, other mechanisms

may be occurring in the chronic phase of these diseases aside from the bacterial infection and related immunological dysfunction, mainly associated with continued, increased inflammation. In this study, we found that patients with lower GIS (grade 0–1, n = 12) showed a shorter disease duration (mean ± SD 38·27 ± 51·51 months) than patients with higher GIS (grade 2–4, n = 51; mean ± SD 68·63 ± 73·67 months). Among the 12 patients with lower GIS values, six had a disease duration of under a year. Many reports have suggested various immunosuppressive agents or specific monoclonal antibodies targeting immune competency as an alternative therapy for recalcitrant and nonresponding cases.[3,5,27–32] From this point of view, the decrease in symptom severity and the achievement of PWNL might have resulted partially from the known immunomodulatory actions of HIG. The known, possible mechanisms of HIG treatment effects are summarized in Table 5. Clinically applicable differences in those immunological functions depending on the various clinical and laboratory conditions have not been elucidated. However, it is not possible to select specific actions that could be responsible for these effects in our patient group.

The immunomodulatory action of HIG is widely known and is reported in other inflammatory diseases such as autoimmune bullous diseases (pemphigus, epidermolysis bullosa, herpes gestationis and linear IgA dermatosis), dermatomyositis, erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis.[15,18] Conventional HIG dosages in these diseases are much higher (2–9 g kg^{-1} per cycle).[15,18] The dosage used in our study was chosen based upon practical experience. In the outpatient clinic environment, intramuscular injection rather than intravenous infusion was preferred by the physicians and patients because it saved time. In general, the involved body surface area was much smaller in our patients in comparison with the other diseases mentioned above that need higher doses of HIG. Thus, we started the treatment with the maximal dose the patients could tolerate by intramuscular injection. The remarkable therapeutic effects obtained with smaller dosages of HIG compared with the conventional recommended dosage could be due to the fact that the involved skin lesions in our study had a smaller area than those indicated in the 'high dose' HIG therapy. In light of the immunomodulatory functions suggested above, it seems reasonable from our study that HIG acts as an 'inducer'. Such a mechanism could occur with relatively decreased serum or tissue concentrations, as opposed to other direct mechanisms of action (for instance, 'antibody neutralizing'), which are known to require much higher HIG concentrations.

Although our study was an open-label trial with a small number of subjects, our results demonstrate that intramuscular HIG may be used for the treatment of recalcitrant suppurative skin diseases as an independent or a combined treatment. We were not able to confirm the efficacy of the treatment according to the pathogen type because bacterial culture and identification were not performed in all of the patients. According to our results, HIG seems to have a universal effect regardless of pathogen. Also, that effect was considered to occur regardless of concomitant therapies or medications. Nevertheless, a controlled study in a larger group with a complete microbiological study should be completed in the future to confirm our results. Meanwhile, although only two indications of HIG related to dermatology have been approved by the U.S. Food and Drug Administration (graft-versus-host disease and Kawasaki disease[17]), the use of intramuscular HIG as an alternative off-label choice seems justifiable, especially in the treatment of chronic, recurrent, and nonresponding cases for which conventional treatments are not effective. With the corroboration by larger, long-term, and randomized studies, we hope that there will be an expansion of dermatological indications for HIG in the future.

Table 5 Known mechanisms of action of human immunoglobulin[a]

Inflammation
Attenuation of complement-mediated damage
Decrease in immune complex-mediated inflammation
Induction of anti-inflammatory cytokines
Inhibition of endothelial cell activation
Neutralization of microbial toxins
Cell growth
Regulation of apoptosis pathways
Inhibition of lymphocyte proliferation
T cells
Regulation of T-cell cytokine production
Neutralization of T-cell superantigens
B cells and antibodies
Control of emergent bone marrow B-cell repertoires
Negative signalling through inhibitory Fcγ receptors
Selective downregulation or upregulation of antibody production
Neutralization of circulating autoantibodies by anti-idiotypes
Mast cells, histamine and leukotrienes
Inhibition of histamine release
Inactivation of released histamine
Protective potential against exogenous histamine-derived shock
Fc receptors
Blockade of Fc receptors on macrophages and effector cells
Induction of antibody-dependent cellular cytotoxicity
Induction of inhibitory Fcγ receptor IIB
Saturation of FcRn

[a]Information in this table is derived from various references.[2,12,14,15,18,33–35]

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